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Recent progress in synthesis of 3-functionalized azetidines

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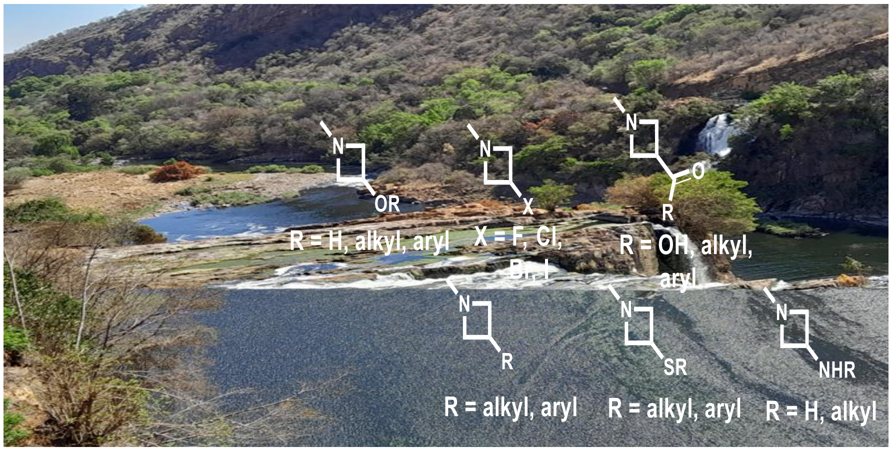
Abstract

Azetidines in general, and the 3-functionalized azetidine motif in particular, occur in nature and are compounds of biological interest. The four-membered rings are highly strained and hence their synthesis is always a challenging endeavour. The ring strain of azetidine ring is exploited for the synthesis of other valuable organic compounds. Several methods have been developed for the synthesis of 3-functionalized azetidines in recent years. These methods include cyclization of appropriate 1,3-difunctionalized compounds, ring enlargement of aziridines, functional group transformations on azetidine-2-ones and azetidine-3-ones, and nucleophilic substitutions on the azetidine rings. The aim of the present article is to review the recent literature on methods for the synthesis of 3-functionalized azetidines such as 3-hydroxy/alkoxy azetidines, 3-acylazetidines, 3-haloazetidines, 3-alkyl/arylazetidines, 3-amino/nitro/azido-azetidines, and 3-sulfur-substituted- and 3-boron-substituted azetidines.



Keywords: azetidines, 3-hydroxyazetidine, 3-haloazetidines, 3-aminoazetidines, 3-nitroazetidines, 3-acyl/alkoxycarbonylazetidines

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1. Introduction

Azacyclobutanes, commonly known as azetidines, are well known heterocyclic compounds of synthetic and biological interest. Though the development of chemistry of azetidines was shadowed by interest in chemistry and biology of its 2-one derivatives known as β-lactams, discovery of some azetidines of potential biological interest has given impetus to research on synthesis and chemistry of azetidines that is evident from some review papers published from time to time on this topic.[1-11]

Azetidine derivatives are known to exhibit anticancer, antibacterial, antischizophrenic, antimalarial, anti-inflammatory, antidiabetic, antiviral, antioxidant, analgesic, and dopamine antagonist activities.[2] Compounds containing azetidine scaffold including 3-functionalized azetidines have also been isolated from natural resources (Figure 1).[12] The synthesis of azetidines has been a challenging endeavour because the ring is highly strained. However, the ring-strain associated with them makes them valuable building blocks in organic synthesis. Chiral azetidines are also used as asymmetric organocatalysts in organic synthesis.[13,14]

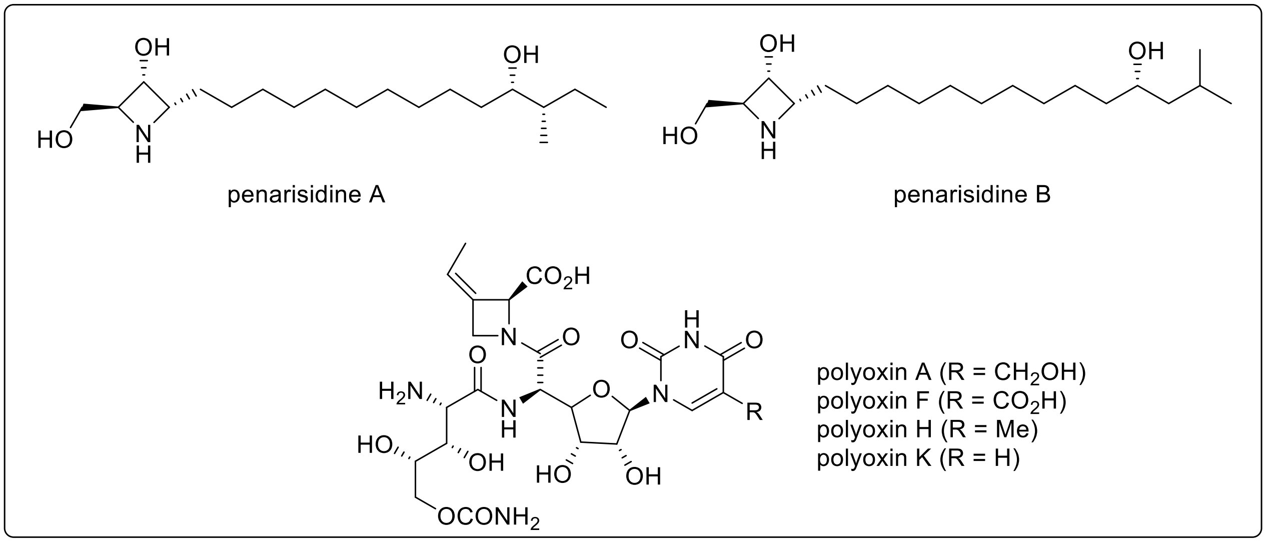


Figure 1. 3-Substituted azetidines of natural origin.

During the review on synthesis and chemistry of azetidines in general,[1] it was noticed that the research on synthesis of 3-functionalized azetidines has drawn considerable interest of the chemists probably because some 3-functionalized azetidines occur in nature and many azetidines of therapeutic importance are functionalized at C-3 of the azetidine ring (Figure 2).[15-23] More recently, Seavill has highlighted the application of 3-functionalized azetidines in synthesis of ring-opened products.[24] They have reported the reactions using 3-functionalized azetidines bearing 1-naphthyl units and cyclohexane carbonyl chloride in 2-methyltetrahydrofuran as an optimum solvent leading to the formation of ring-opened products in high yields and enantiomeric excess.[18]

It was, therefore, considered pertinent to review the literature on the synthesis of 3-functionalized azetidines. The present article thus reviews the synthesis of azetidines such as 3-alkoxy/hydroxy-, 3-halo-, 3-nitro/amino, 3-alkyl/aryl, and 3-acyl/alkoxycarbonyl substituted azetidines reported from 2015-2024 with focus on literature during last five years from 2020 to 2024. However, some pioneering work and newer papers reported outside this time framework are also cited. Synthesis of azetidine-2-ones or azetidine-3-ones is not discussed here because it is beyond the scope of this review.

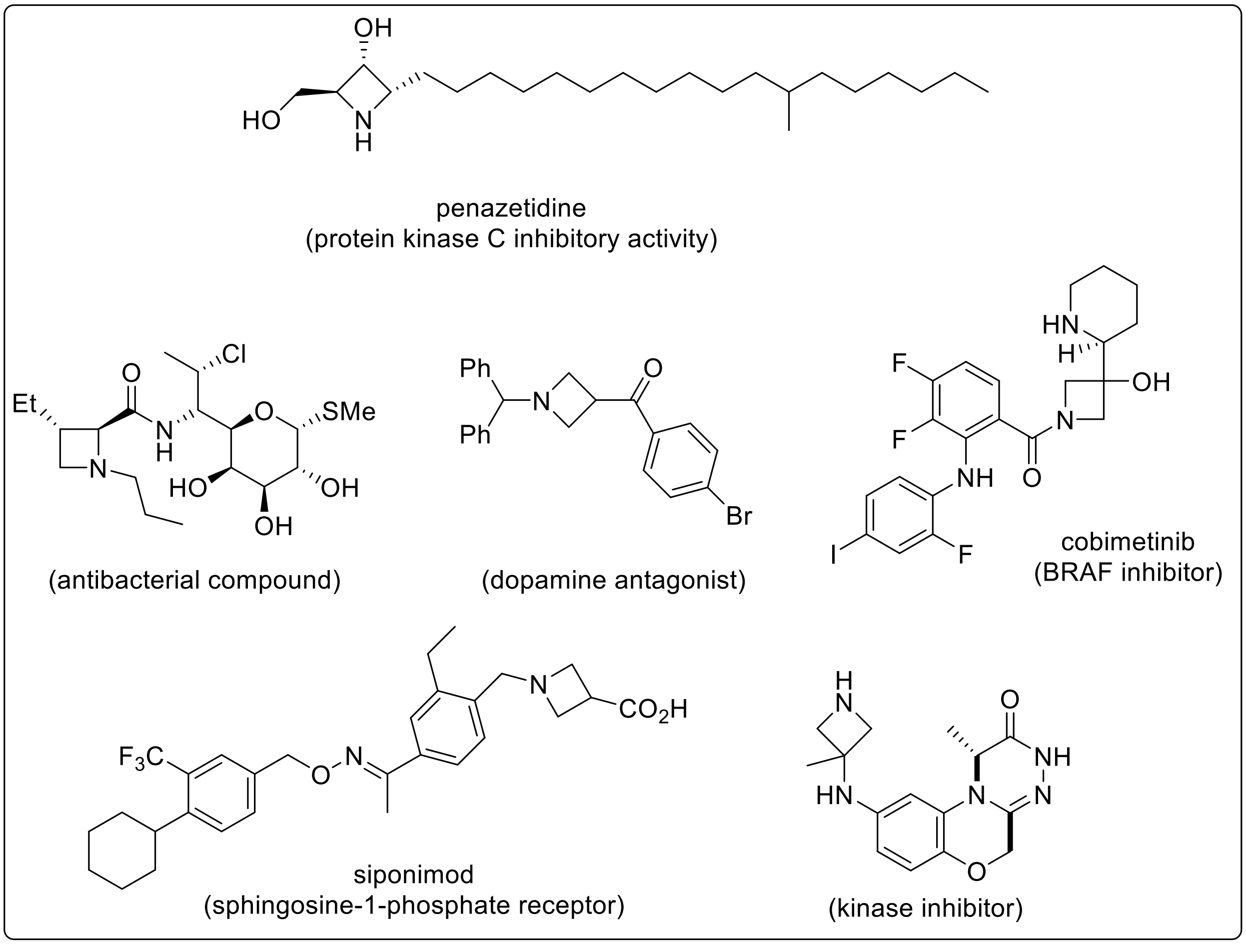


Figure 2. Biologically important 3-substituted azetidines.

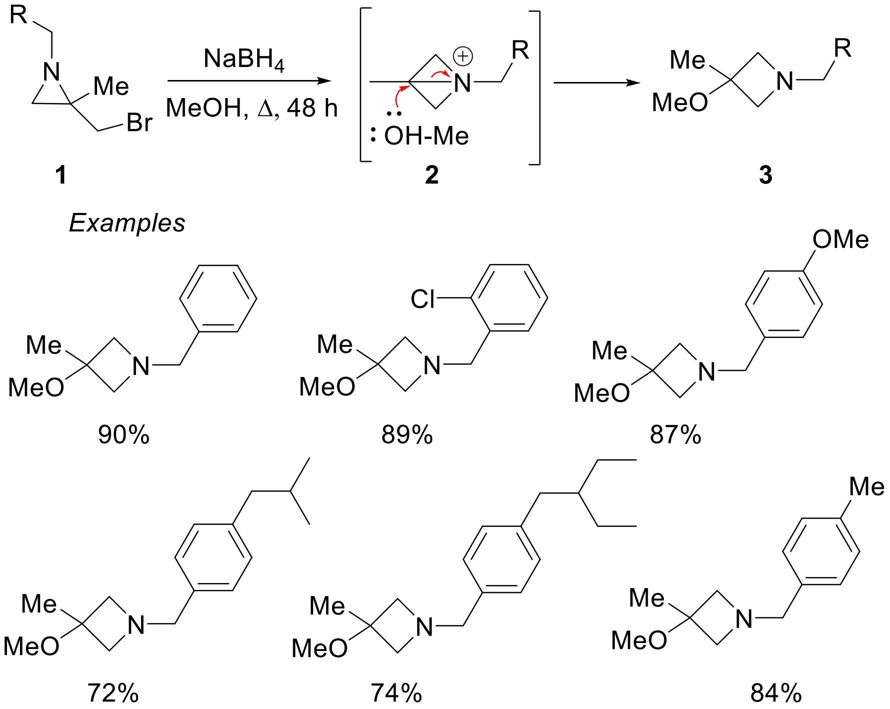
2. Synthesis of 3-Functionalized Azetidines

The common methods for the synthesis of azetidines include cycloaddition reactions and cyclizations of 1,3-aminoalcohols, 1,3-aminoethers, 1,3-aminosulfonates, and 1,3-haloamines, etc.[1] The reduction of 2-

azetidinones and other functional group transformations on the azetidine ring also serves prominently in synthesizing diverse azetidines. The ring-strain-release strategy starting from aziridines has become increasingly popular in synthesis of azetidines. In principle, 3-functionalized azetidines can be synthesized using these methods by taking appropriately functionalized substrate(s). The succeeding sub-sections review the synthesis of 3-alkoxy/hydroxyazetidines, 3-acyl/alkoxycarbonylazetidines, 3-haloazetidines, 3-alkyl/arylazetidines, 3-alkylthio/arylthioazetidines, azetidine-3-boronates , and 3-nitro/azido/aminoazetidines.

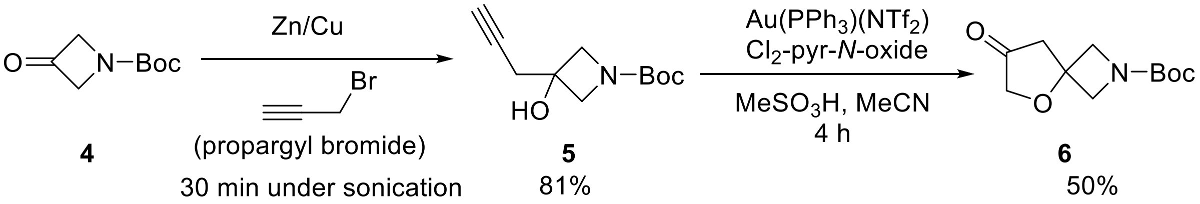
2.1. Synthesis of 3-alkoxy- and 3-hydroxyazetidines

Among 3-functionalized azetidines, 3-hydroxyazetidines are widely investigated. A novel synthesis of 3-methoxy-3-methyl-1-alkylazetidines by rearrangement of 1-alkyl-2-bromomethyl-2-methylaziridines **1** on treatment with sodium borohydride in methanol was reported.[25] Aziridines react with sodium borohydride to generate a bicyclic intermediate **2** that undergoes ring-opening by nucleophilic attack of methanol to furnish the N-substituted 3-methoxy-3-methylazetidines **3** (Scheme 1).



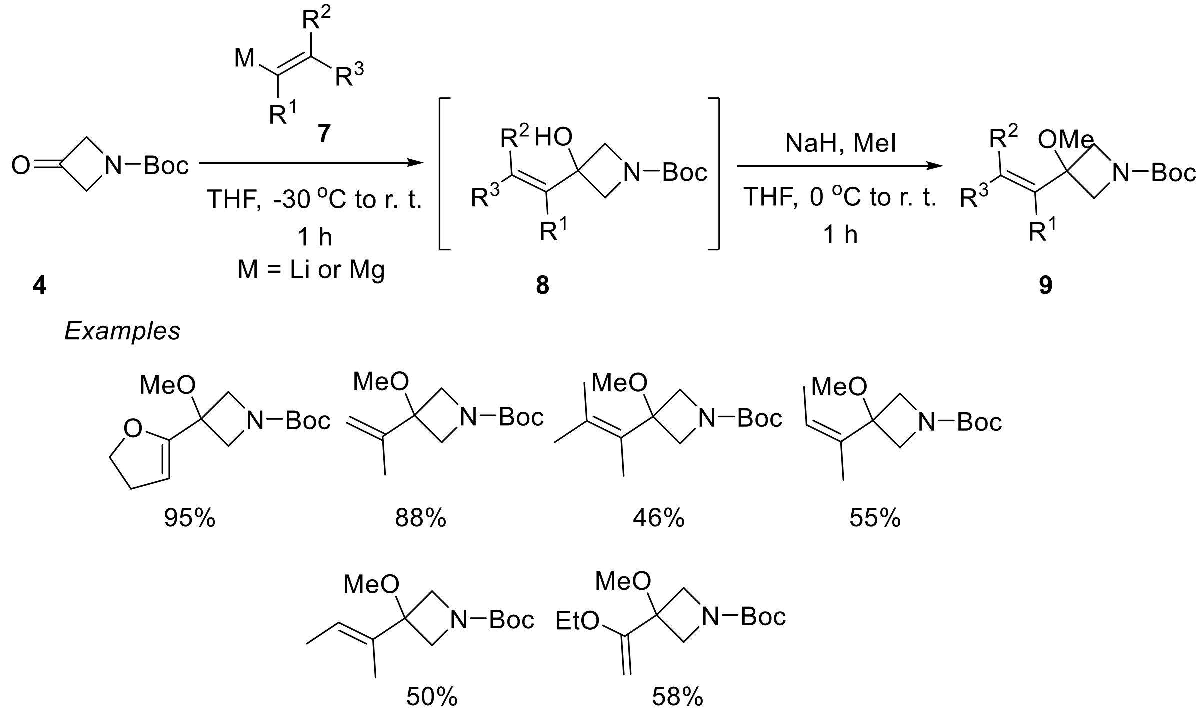
Scheme 1. Synthesis of 3-alkoxyazetidines from aziridines.

An interesting synthesis of 3-spirocyclic azetidines is reported starting from *N*-Boc-3-oxoazetidine **4.** The reaction of later compound with a zinc/copper couple in the presence of propargyl bromide yields *N*-Boc-3-hydroxy-3-(prop-2-yn-1-yl)azetidine **5** (Scheme 2).[26] Azetidine **5** reacts with a catalytic amount of Au(PPh$_3$)(NTf)$_2$ in the presence of 3,5-dichloropyridine-*N*-oxide and methanesulfonic acid leading to the formation of spirocyclic azetidine **6**.



Scheme 2. Synthesis of a spiro-fused azetidine starting from N-Boc azetidine-3-one.

Recently, a synthesis of 3-methoxy-3-vinylazetidines **9** has been developed by reaction of alkenyl metal species **7** with *N*-Boc-3-oxoazetidine **4**.[27] The corresponding azetidine products **8** were treated with methyl iodide and NaH without any further purification leading to methylation of the alcohol group forming the final product (Scheme 3). These 3-vinylazetidines serve as starting material for the synthesis of fused tricyclic and tetracyclic 2- and 3-alkylideneazetines with up to four contiguous stereocenters. Metallation of vinylazetidines using *s*-butyllithium generates the key azetinyllithium intermediate that undergoes [4+2]-cycloaddition with electron-deficient dienophiles such as maleic anhydride and *N*-substituted maleimides furnishing fused azetidines (Figure 3).



Scheme 3. Synthesis of 3-methoxy-3-vinylazetidines from alkenyl metal species and *N*-Boc-3-oxoazetidine.

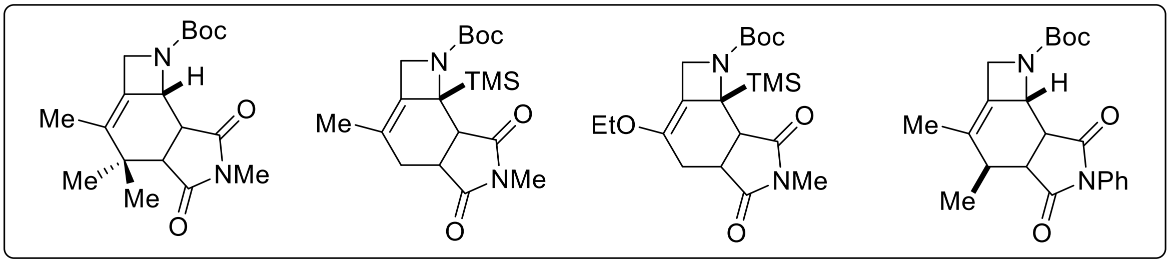
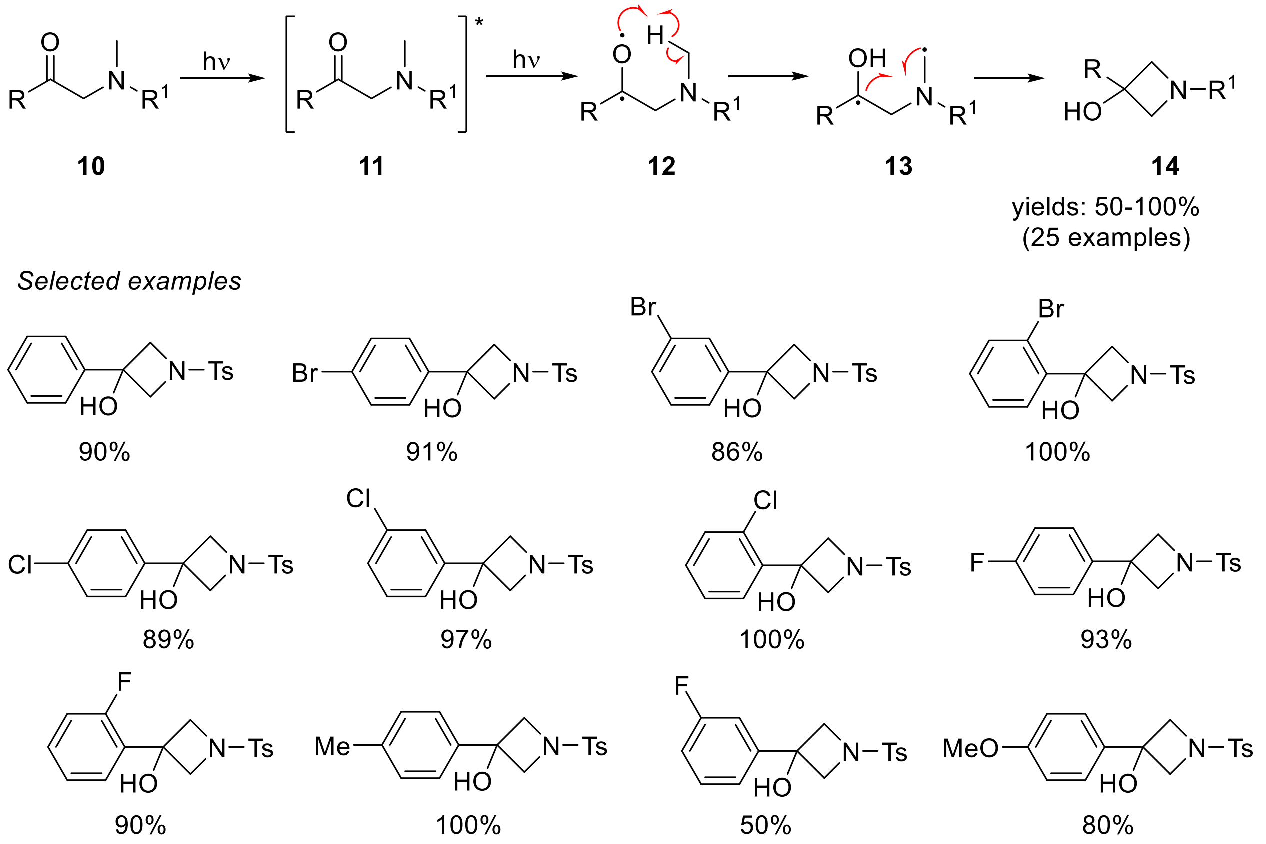


Figure 3. Some fused azetidines obtained using vinylazetidines as building blocks.

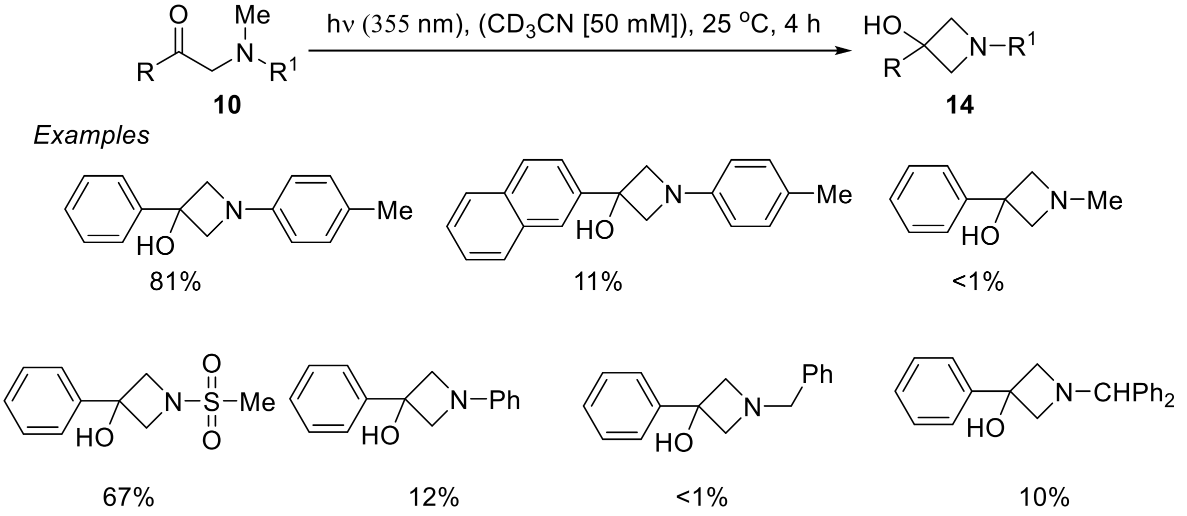
Rugerri and co-workers employed the photo-flow Norrish-Yang cyclization of 2-aminoketones **10** furnishing 3-hydroxyazetidines in good yields (86-100%) with the exception of an aminoketone bearing a 3-fluorophenyl ketone that offered only a 50% yield.[28] The reaction occurs *via* an excited state intramolecular cyclization of a simple acyclic 2-aminoketone precursor **10.** Photochemical excitation involving a *n*→π* transition (**10**→**11**) leads to the transient intermediate oxygen-centered radical **12**, followed by a 1,5-hydrogen abstraction step leading to a new 1,4-diradical intermediate **13** which combines to form the azetidine scaffold **14** (Scheme 4).



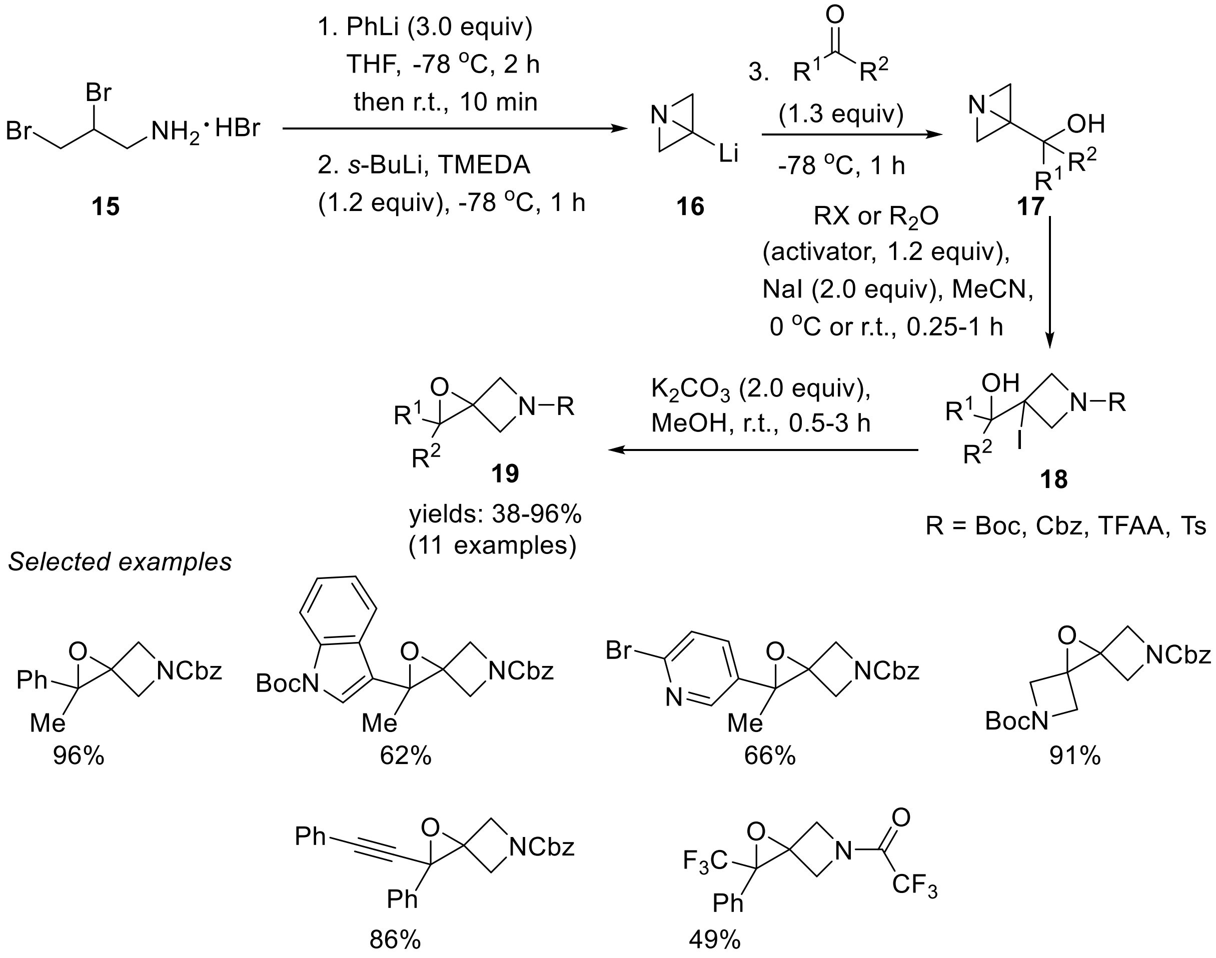
Scheme 4. 3-Hydroxyazetidine ring formation *via* the Norrish-Yang reaction.

The Norrish-Yang cyclization of α-aminoacetophenones (**10**) has been employed by Magg and coworkers for the synthesis of 3-aryl-3-azetidinols (**14**).[29] A yield of 81% was obtained when the *p*-toluenesulfonyl (Ts) group was used as a protecting group at nitrogen. Acetophenone was obtained as a side product in the reaction. However, the reaction was sensitive to electronic and steric factors on protecting group and resulted in low conversions (Scheme 5).

The pioneering work investigating strain-release spirocyclization reactions of azabicyclo[1.1.0]butanes (ABB) allowed access to spiroepoxy azetidines in addition to keto azetidines.[30] First, ABB-Li **16** was generated *in situ* by the sequential reaction of 2,3-dibromopropylamine hydrobromide **15** with phenyllithium and *sec*-butyllithium.[31] Subsequent reaction of **16** with acetophenones at -78 °C formed ABB-carbinols **17** in good yields. Treating ABB-carbinols **17** with less electrophilic activating agents such as CbzCl, TsCl, Boc_2O in the presence of NaI resulted in the formation of α-iodohydrins **18** that are easily converted into spiroepoxy azetidines **19** *via* a base-mediated intermolecular cyclization (Scheme 6). It is worth mentioning that the rate of cyclization decreases drastically for less substituted carbinols.

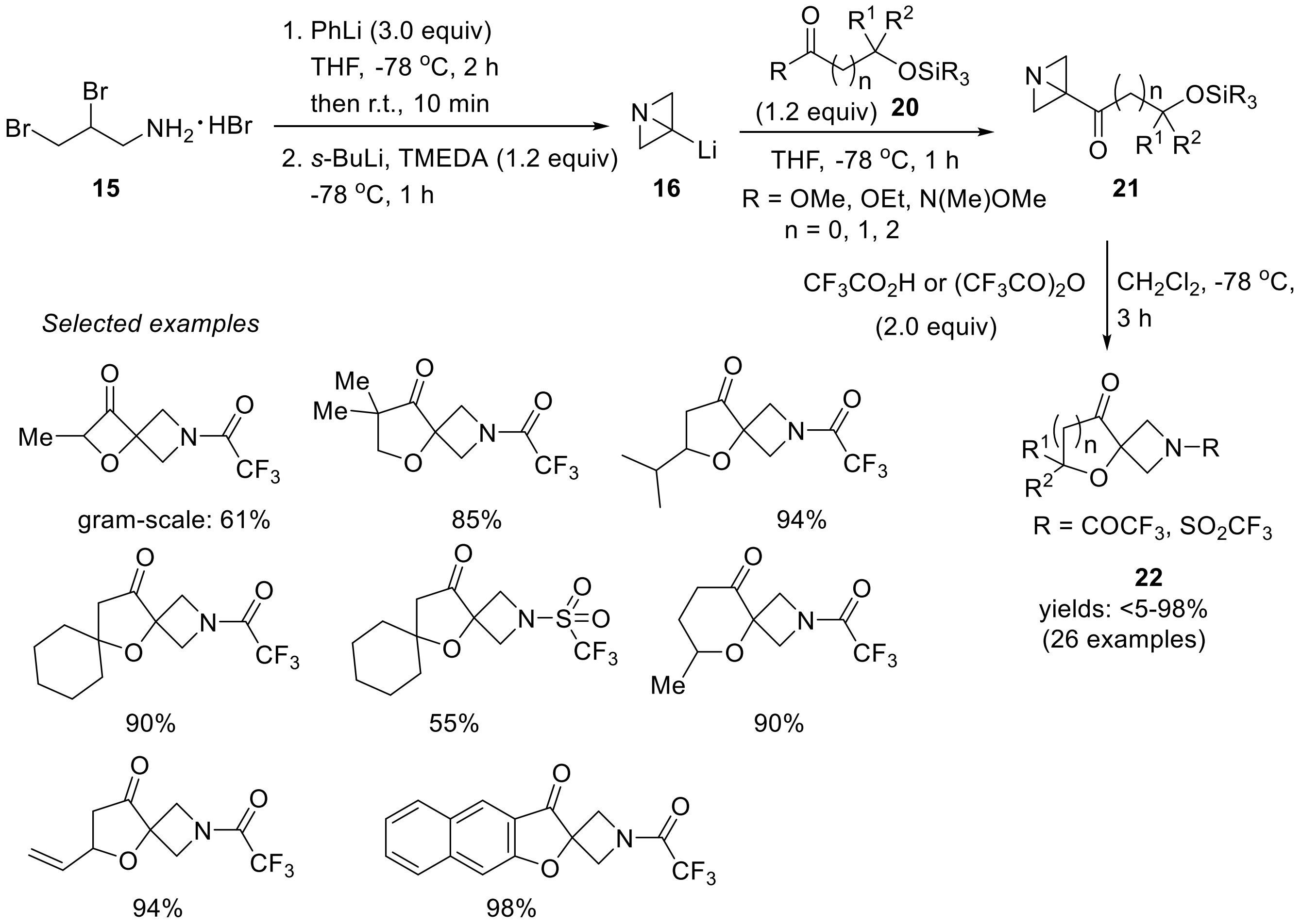


Scheme 5. 3-Hydroxyazetidine ring formation *via* the Norrish-Yang cyclization.



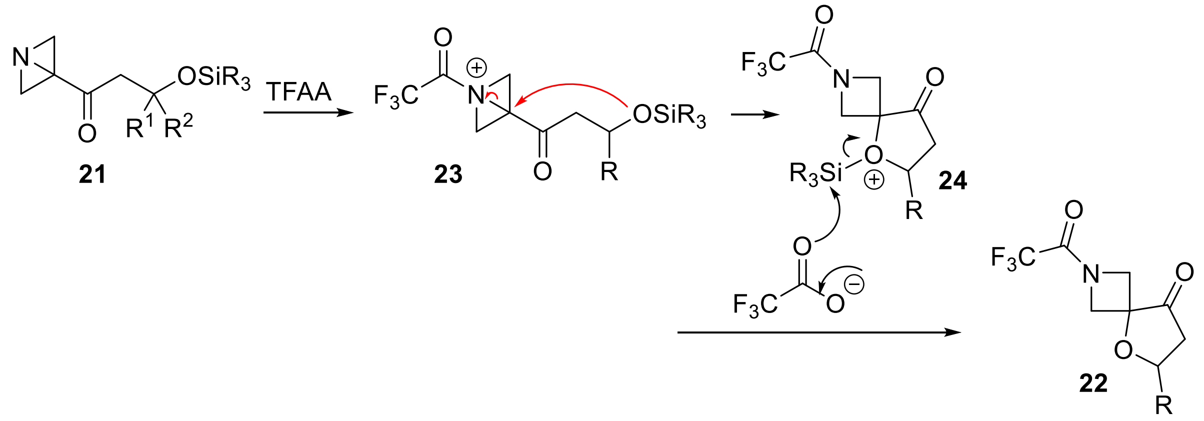
Scheme 6. Formation of *N*-substituted spiroepoxy azetidines from azabicyclo[1.1.0]butyl carbinols.

The Aggarwal group also reported spirocyclization of azabicyclo[1.1.0]butyl ketones, where freshly prepared ABB-Li **16** was treated with either esters or Weinreb amides bearing a silyloxy group in α-, β-, γ-, or δ- positions **20** to furnish azabicyclo[1.1.0]butyl ketones **21** (Scheme 7).[32] The use of trifluoroacetic acid or trifluoroacetic anhydride successfully furnished the spirocyclic products in good yields, while Lewis acids such as boron trifluoride failed in inducing spirocyclization. This method allowed for the synthesis of a variety of spiro-azetidines **22** that incorporated 4-, 5-, or 6-membered rings as well as benzo-fused ring systems.



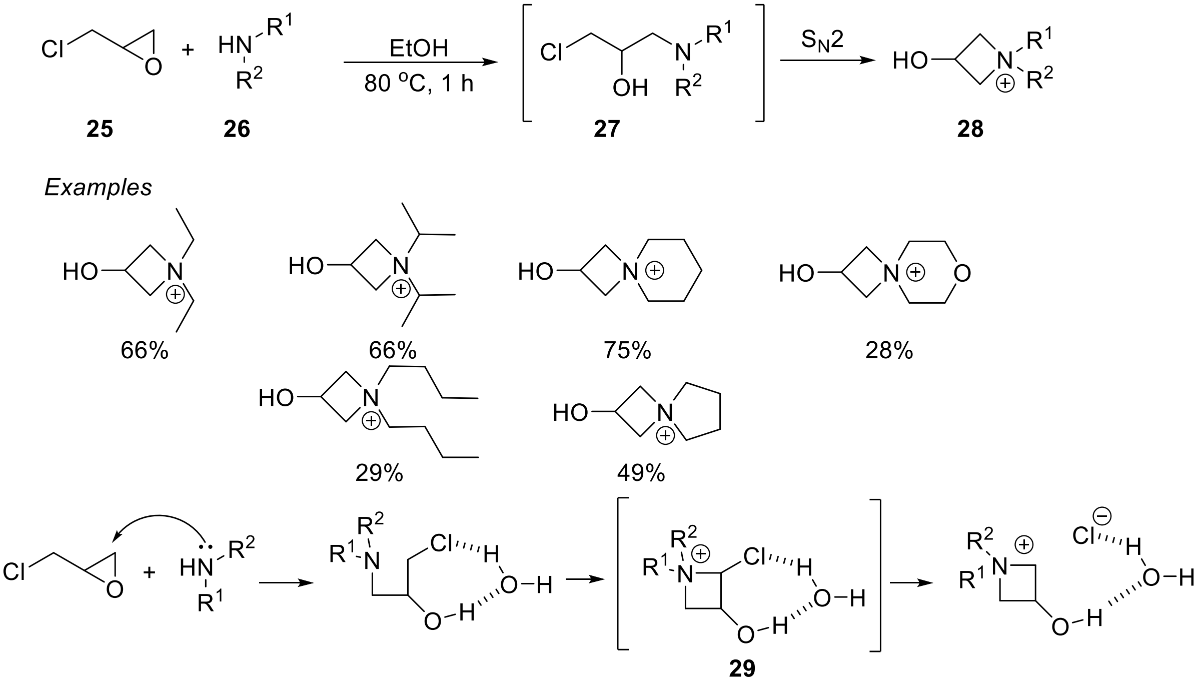
Scheme 7. Synthesis of azetidines spiro-fused at its C-3 with 4-6 membered rings.

The most plausible mechanism for the formation of spirocyclic products **22** involves generation of trifluoroacyl ammonium intermediate **23** upon acylation of the ABB nitrogen of **21** that activates the bridgehead carbon towards nucleophilic substitution (Scheme 8). A strain-release-driven intramolecular attack of the silyl ether on bridgehead carbon of the ABB leads to the construction of the challenging spiro-center to give oxonium ion intermediate **24**. After spirocyclization, cationic intermediate **24** may undergo a trifluoroacetate-promoted desilylation to furnish the spirocyclic product **22**.[33-37]



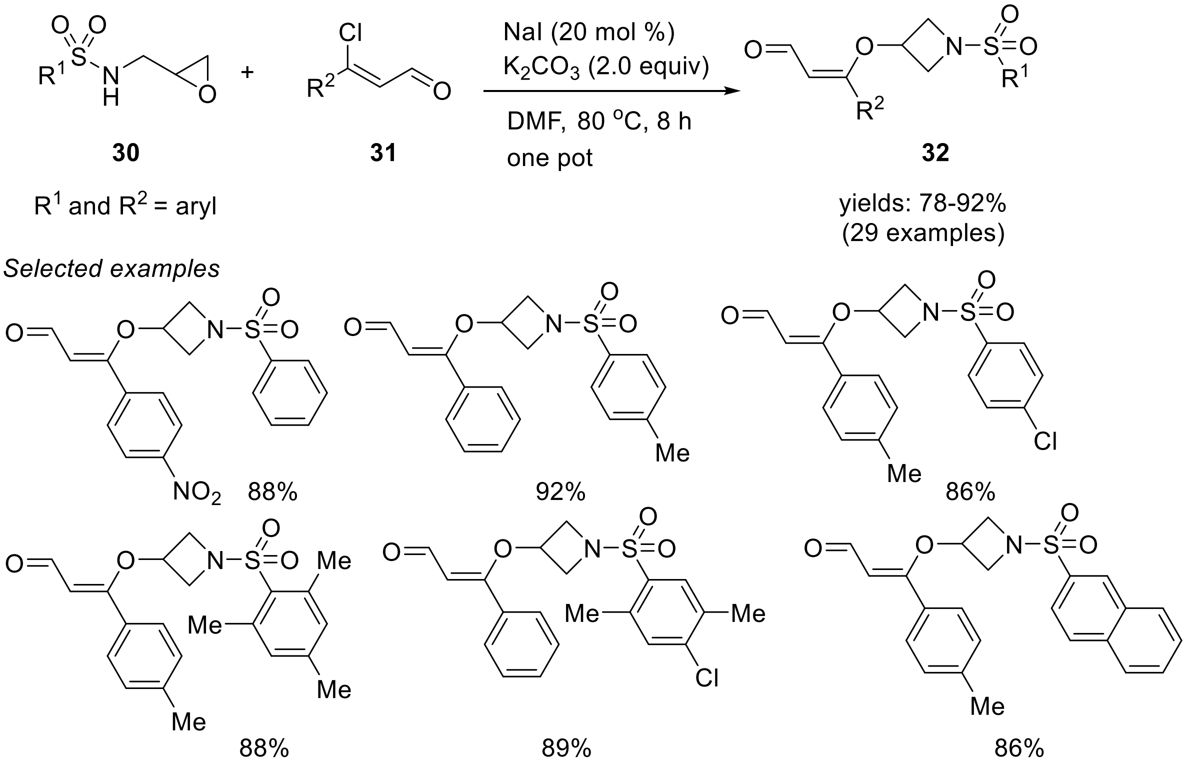
Scheme 8. Mechanism of strain-release spirocyclization of azabicyclo[1.1.0]butyl ketones.

Sivo and co-workers recently developed a flow method that is highly efficient in furnishing 3-hydroxyazetidinium salts in good yields.[38] In this protocol, the reaction starts with the aminolysis of epichlorohydrin **25** with dialkylamines **26** to give 1-chloro-*N*,*N*-(dialkylamino)propan-2-ol intermediate **27**, which spontaneously undergoes an intramolecular cyclization *via* S_N2 eaction at C-1, giving the corresponding *N*,*N*-(dialkyl)-3-hydroxyazetidinium salts **28** in 28-75% yield (Scheme 9). Mechanistically, 1-chloro *N*,*N*-(dialkylamino)propan-2-ol intermediates **29** formed, rearrange quickly giving the final azetidinium products.

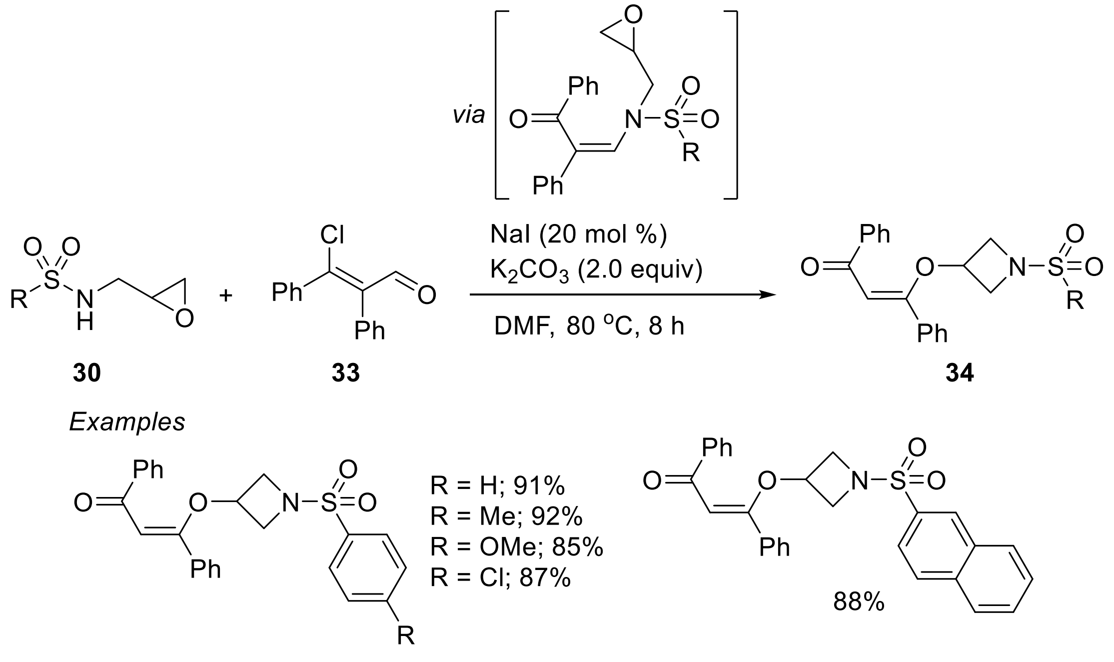


Scheme 9. Synthesis of 3-hydroxyazetidinium salts by aminolysis of epichlorohydrin.

Recently, a method that utilizes enamides, derived from *N*-oxiranylmethylbenzenesulfonamides **30**, reacted with β-chlorocinnamaldehyde **31** to form 3-functionalized azetidines **32** in up to 92% yield in one pot by ring expansion has been reported (Scheme 10).[39] However, use of an α-substituted β-chlorocinnamaldehyde **33** yielded azetidines with an α,β-unsaturated ketone moiety **34** instead of the aldehyde moiety (Scheme 11). It was demonstrated that the initial reaction of β-chlorocinnamaldehyde is essential to drive the reaction *via* an epoxy-enamide intermediate since *N*-oxiranylmethylbenzenesulfonamide **35** itself did not convert to azetidine.

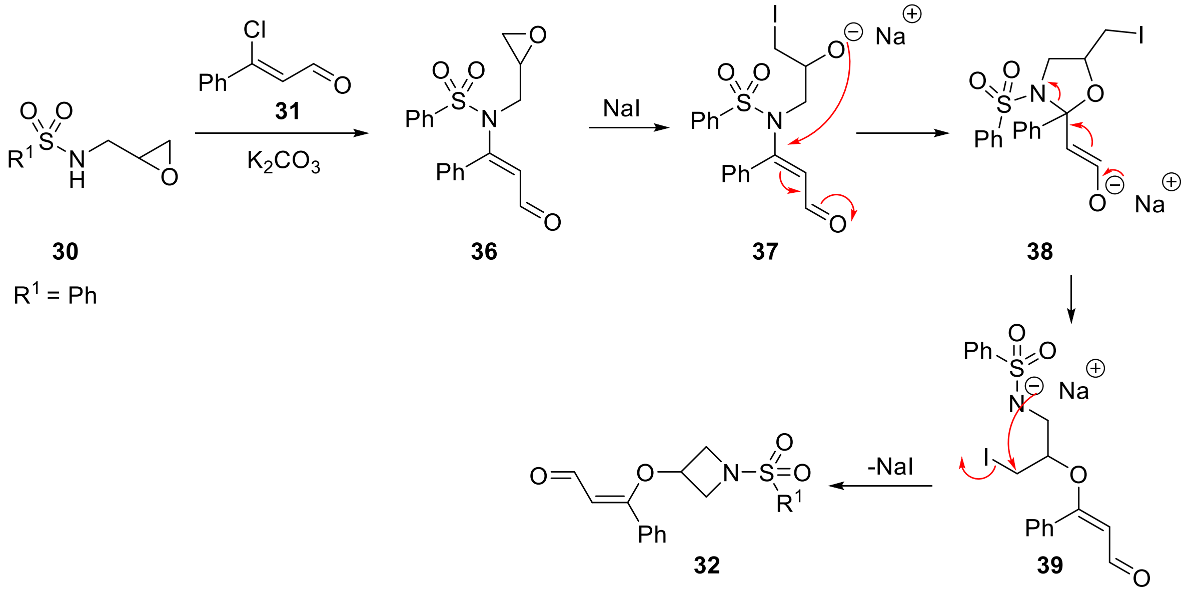


Scheme 10. Synthesis of 3-alkoxyazetidines from *N*-oxiranylmethylbenzenesulfonamides and β-chlorocinnamaldehyde.



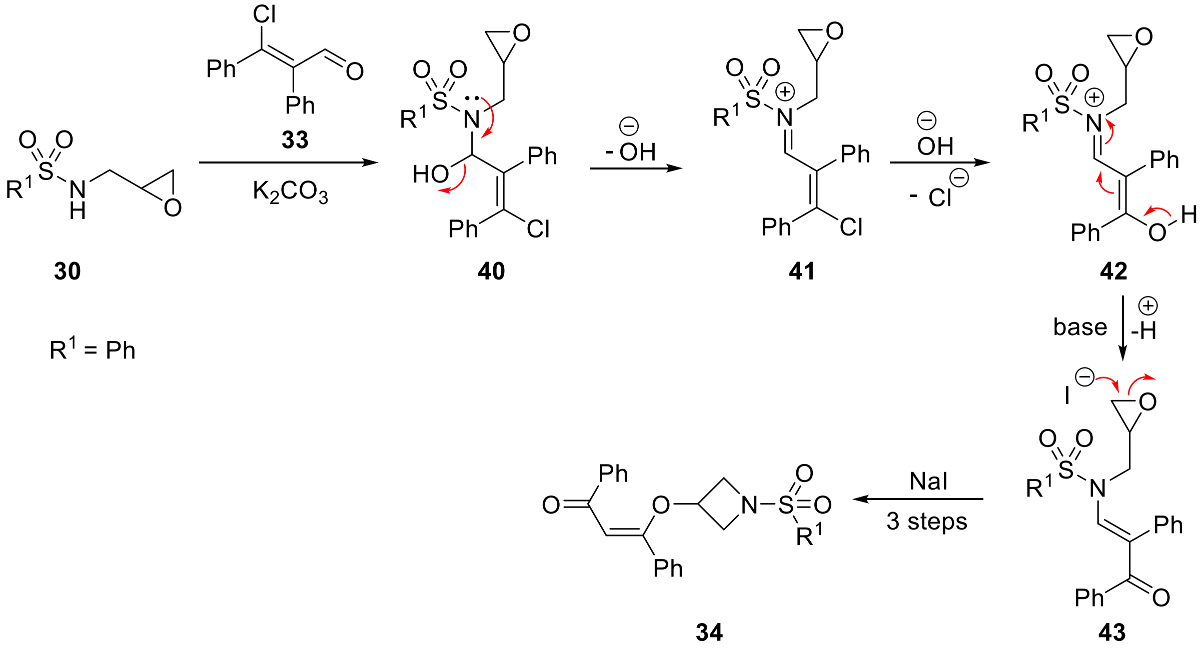
Scheme 11. Synthesis of 3-alkoxyazetidines from *N*-oxiranylmethylbenzenesulfonamides and α-substituted β-chlorocinnamaldehyde.

According to the proposed pathway for the formation of **32**, *N*-oxiranylmethylbenzenesulfonamide **30** reacts with β-chlorocinnamaldehyde **31** to form the enamide intermediate **36**, which undergoes attack of iodide on the epoxide ring to afford **37**. Intermediate **37** leads to intermediate **38** *via* an intramolecular oxa-Michael addition type of reaction. Reverse polarization of intermediate **38** followed by C-N bond cleavage leads to formation of species **39** by 4-*exo-tet* cyclization, yielding product **32** by the elimination of NaI (Scheme 12).



Scheme 12. Mechanism of reactions shown in Scheme 10.

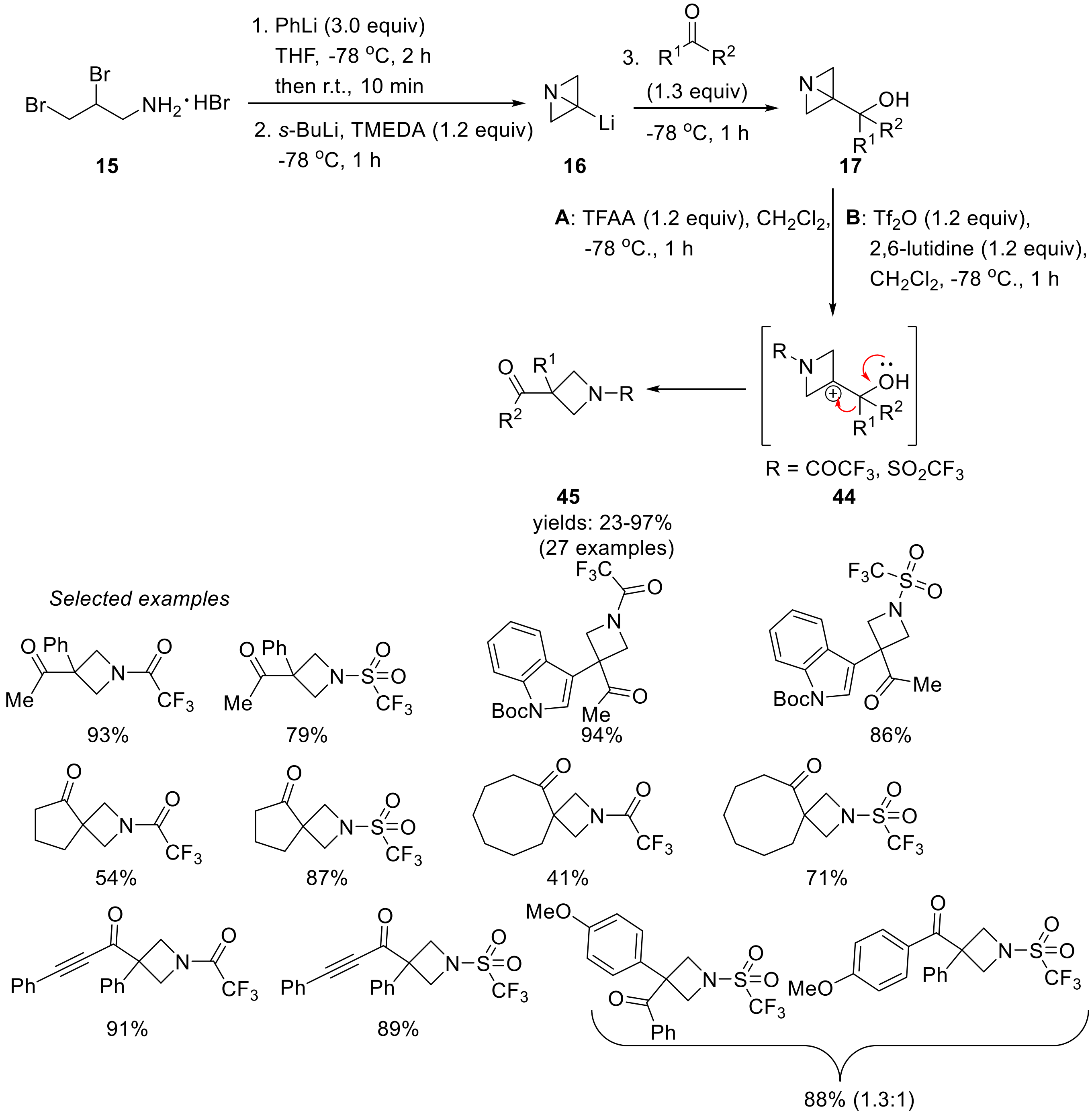
A different pathway has been suggested for formation of products **34** whereby *N*-oxiranylmethylbenzenesulfonamide **30** reacts with α-phenyl β-chloro-cinnamaldehyde **33** to give addition product **40.** Elimination of the hydroxyl group (E1cB), followed by substitution of chloro group with the hydroxyl group affords iminium ion **42** *via* **41**. The substitution at Sp2 carbon is presumably facilitated by high temperature (80 °C) used in this case. Elimination of the proton from intermediate **42** gives **43**. Subsequent steps leading to product **34**, assuming a possible C-C bond rotation (Scheme 13) that involves species like **36**, **37**, and **38**.



Scheme 13. Mechanism of reaction between *N*-oxiranylmethylbenzenesulfonamide with α-phenyl β-chloro-cinnamaldehyde.

2.2. Synthesis of azetidines with carbonyl groups on C-3

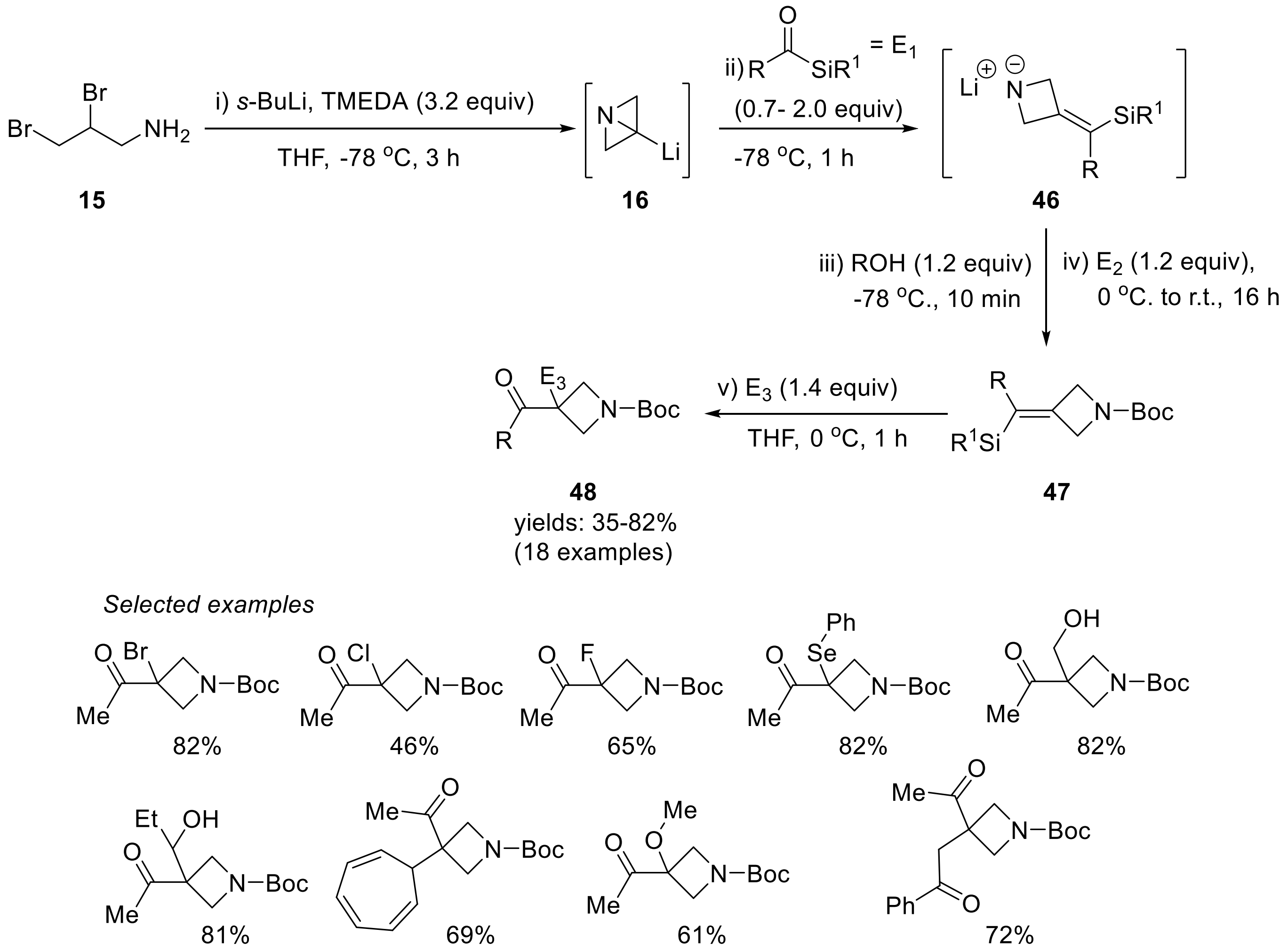
Azetidines bearing carbonyl groups on C-3 may serve as valuable building blocks for the synthesis of diverse azetidine-tethered motifs utilizing the reactivity of carbonyl groups. In their pioneering work investigating strain-release spirocyclization reactions of azabicyclo[1.1.0]butanes (Scheme 6), the Aggarwal group reported access to acyl/alkoxycarbonyl-substituted azetidines through semi-pinacol rearrangements of azabicyclo[1.1.0]butyl carbinols (ABB-carbinols).[30] First, the ABB-Li **16** is formed *in situ* by the sequential reaction of 2,3-dibromopropanamine hydrobromide **15** with phenyllithium and *sec*-butyllithium and subsequently reacted with a range of aldehydes and ketones at -78 °C to form ABB-carbinols **17**.[25] Treatment of ABB-carbinols with trifluoroacetic anhydride (TFAA; Method A) or triflic anhydride (Tf$_2$O; Method B) triggers a semi-pinacol rearrangement to give keto *N*-substituted 3-acylazetidines **45** *via* intermediate **44**. The protocol utilizing Tf$_2$O requires the use of 2,6-lutidine for the effective migration of the alkyl or aryl groups (Scheme 14).



Scheme 14. Synthesis of 3-acylazetidines through semi-pinacol rearrangements of azabicyclo[1.1.0]butyl carbinols.

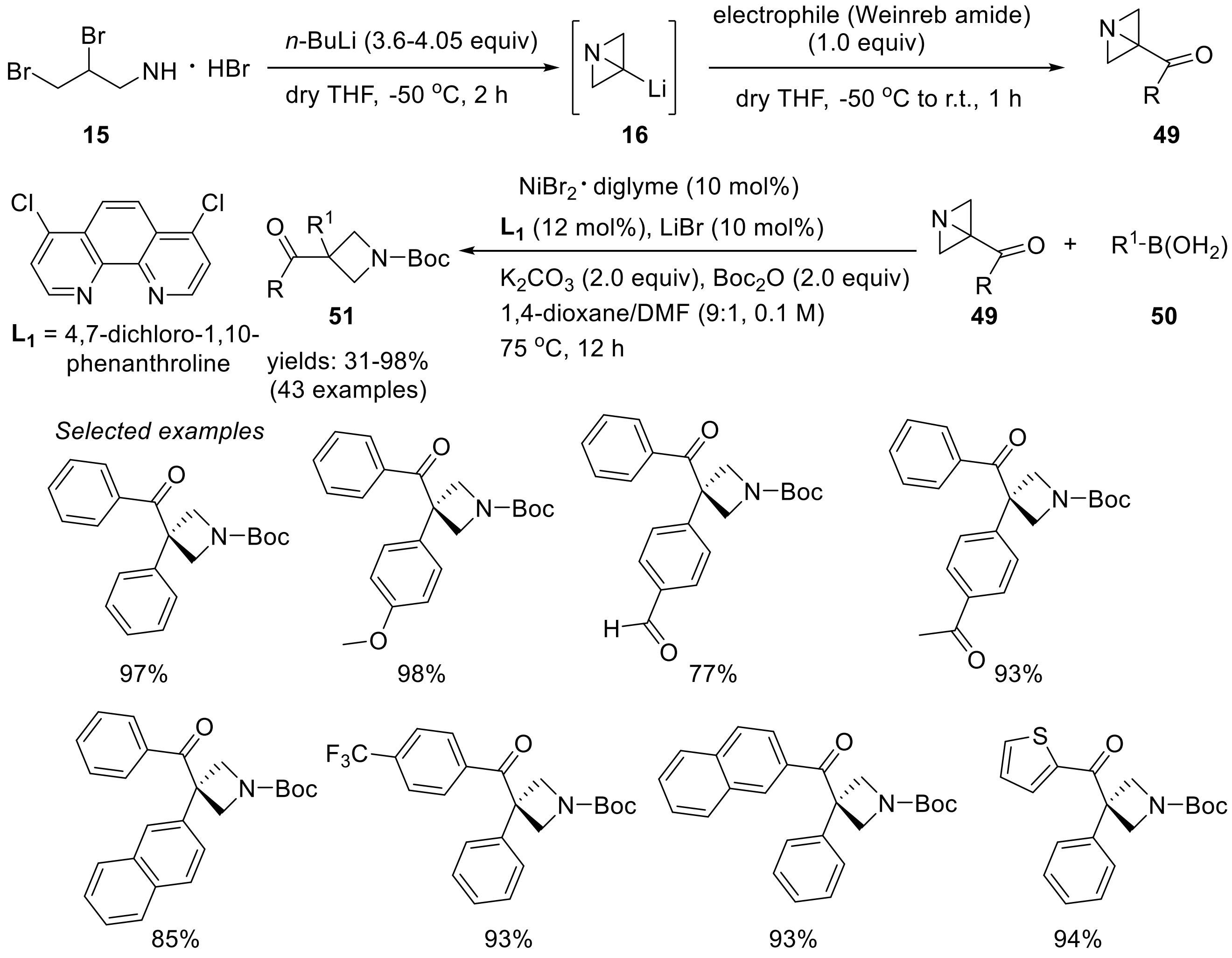
It is worth noting that the nature of the electrophile used for nitrogen functionalization strongly influenced the reaction yield and selectivity. In most cases, the treatment with Tf_2O resulted in higher yields than when TFAA was used. Furthermore, the migration of aryl groups was favored when compared to alkyl groups as usual in pinacol rearrangements, and the reaction generally proceeded with excellent selectivity, when TFAA was used. Moreover, the observed relative migratory aptitude in the semi-pinacol rearrangement was aryl > alkenyl > hydride > more substituted alkyl > less substituted alkyl. Although a similar pattern was observed with Tf_2O, a loss of selectivity was reported since Tf_2O induces a faster reaction.

Recently, the Aggarwal group reported a unique four-component [1,2]-Brook rearrangement protocol that allows the expeditious assembly of N/C3-functionalized azetidines.[40] Coupling of ABB-Li **16**, prepared from commercially available 2,3-dibromopropylamine **15**, with acyl silanes (E_1) gives an alkoxide intermediate which undergoes a [1,2]-Brook rearrangement to generate a carbanion that instantly collapses to open the central bond of the ABB fragment giving lithium amide **46**.[41-43] Protonation of nitrogen in **46** on treatment with alcohol followed by reaction with Boc_2O (E_2) at the nitrogen atom affords azetidines **47**. A further reaction with carbon or heteroatom-based electrophiles (E_3) at the newly installed silyl enol ether gives an overall four-component synthesis of 3-carbofunctionalized azetidines **48** (Scheme15).



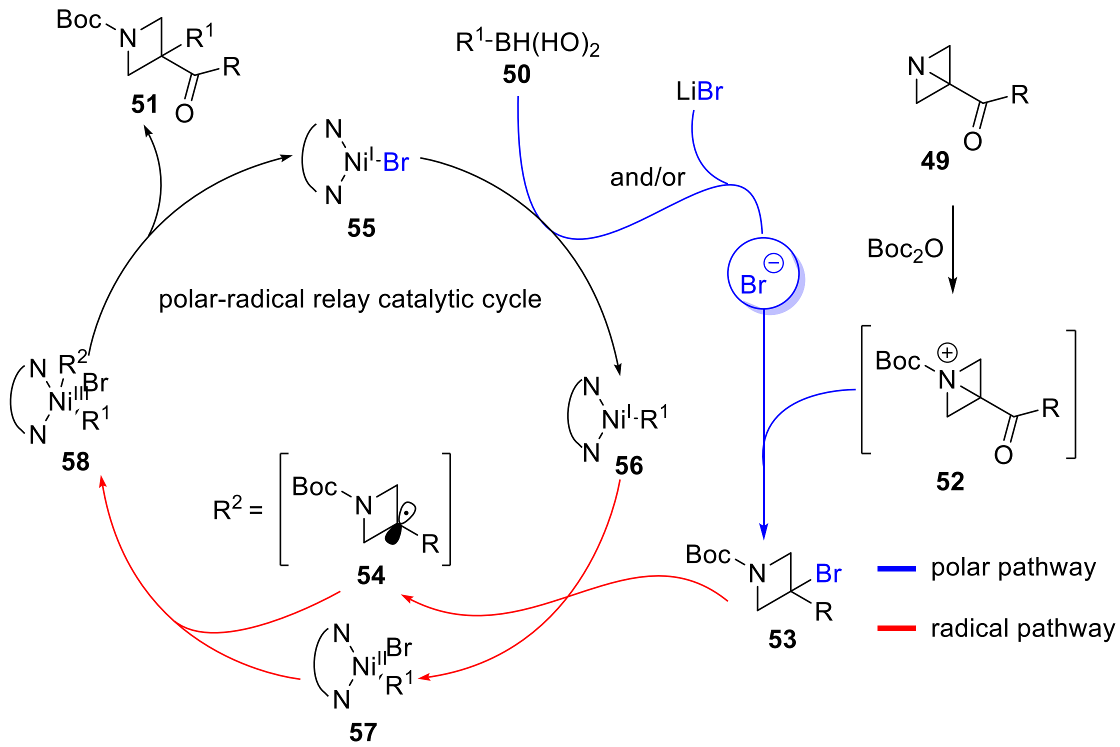
Scheme 15. A four-component [1,2]-Brook rearrangement protocol for the assembly of N/C3-functionalized azetidines.

Recently, a novel one-pot method through a polar-radical relay strategy with broad scope and excellent functional group tolerance for the synthesis of 3,3-dicarbo-functionalized azetidines **51** in good to excellent yields has been developed.[44] The method involves the ring-strain- release and nickel-complex-catalyzed Suzuki Csp^2–Csp^3 cross-coupling of carbonyl ABBs **49** with aryl boronic acids **50** (Scheme 16). The ABB substrates **49** are synthesized from the commercially available 2,3-dibromopropylamine **15** *via* intermediate **16** as shown in previous schemes.



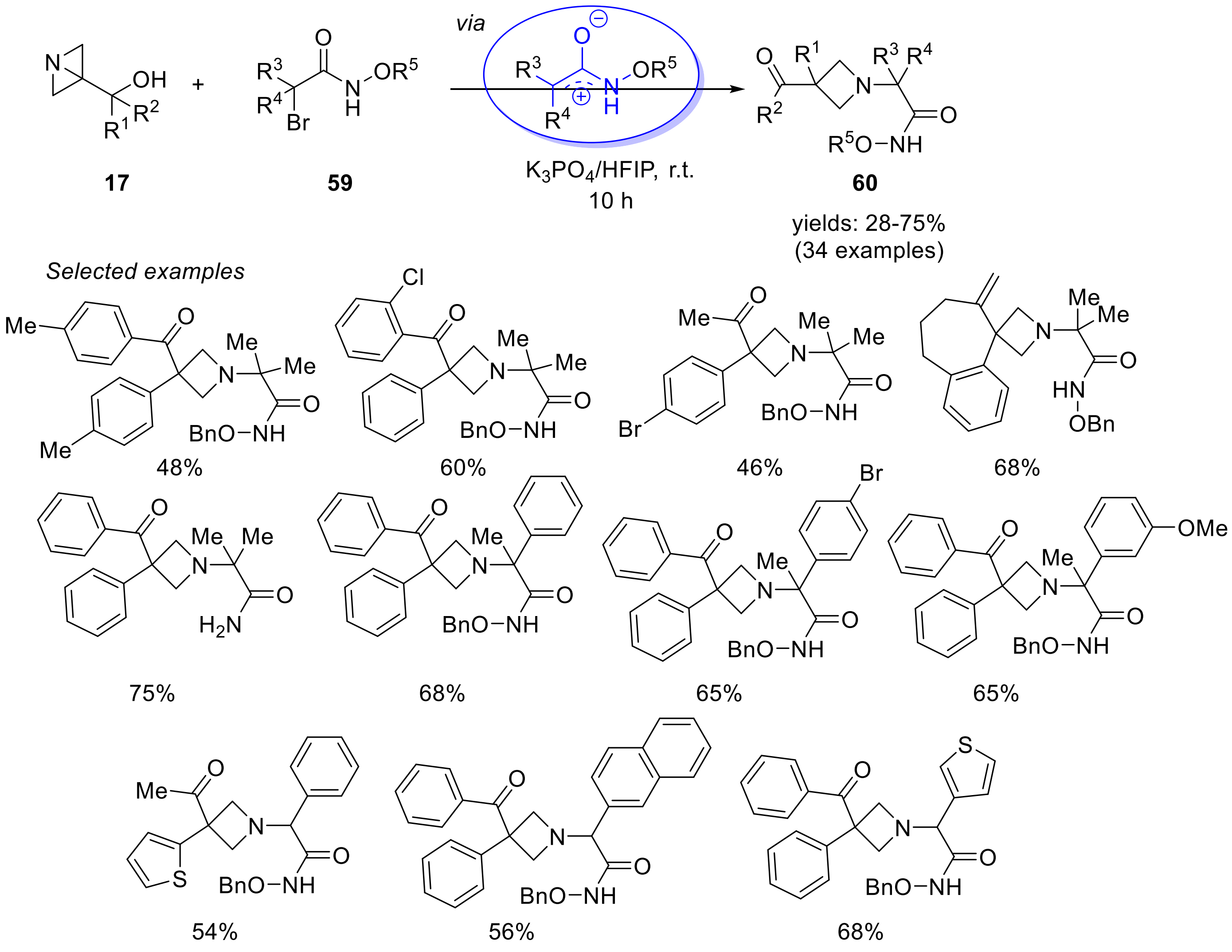
Scheme 16. Synthesis of 3,3-dicarbofunctionalized azetidines through a polar-radical relay strategy.

Preliminary mechanistic studies suggested that the catalytic cycle is kicked off by the comproportionation of Ni$^{(0)}$ and Ni$^{(II)}$ species to give the active Ni$^{(I)}$-Br complex **55**,[45,46] followed by transmetalation of aryl boronic acid **50** with Ni$^{(I)}$-Br complex **55** to afford aryl-Ni$^{(I)}$ complex **56** (Scheme 17). Alongside, catalytic amounts of bromide, either from LiBr or NiBr$_2$·diglyme, relieve the ring strain of Boc-activated benzoyl ABB **52** *via* a polar pathway, forming *in situ* the redox-active species **53**. Reduction of intermediate **53** by aryl-Ni$^{(I)}$ complex **56** leads to azetidinyl radical **54** while concomitantly liberating Ni$^{(II)}$-bromide complex **57**. Recombination of the azetidinyl radical **54** to Ni$^{(II)}$ complex **57** furnishes Ni$^{(III)}$ intermediate **58** which finally creates the C3 all-carbon quaternary-center-containing azetidine **51** following facile decomposition *via* reductive elimination along with the regeneration of the active Ni$^{(I)}$ species **55**.



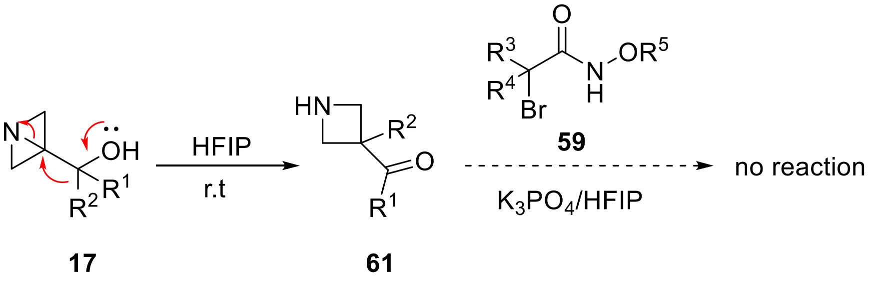
Scheme 17. A proposed reaction mechanism for Scheme 16.

Recently, a versatile cation-driven activation strategy for an ABBs-based access to 1,3-difunctionalized azetidines has been developed.[47] In this strategy, the reaction of azabicyclo[1.1.0]butyl carbinol **17** with α-halohydroxamate **59** using K_3PO_4 as a base and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as a solvent at room temperature furnished N/C3-functionalized azetidines **60** (Scheme 18).



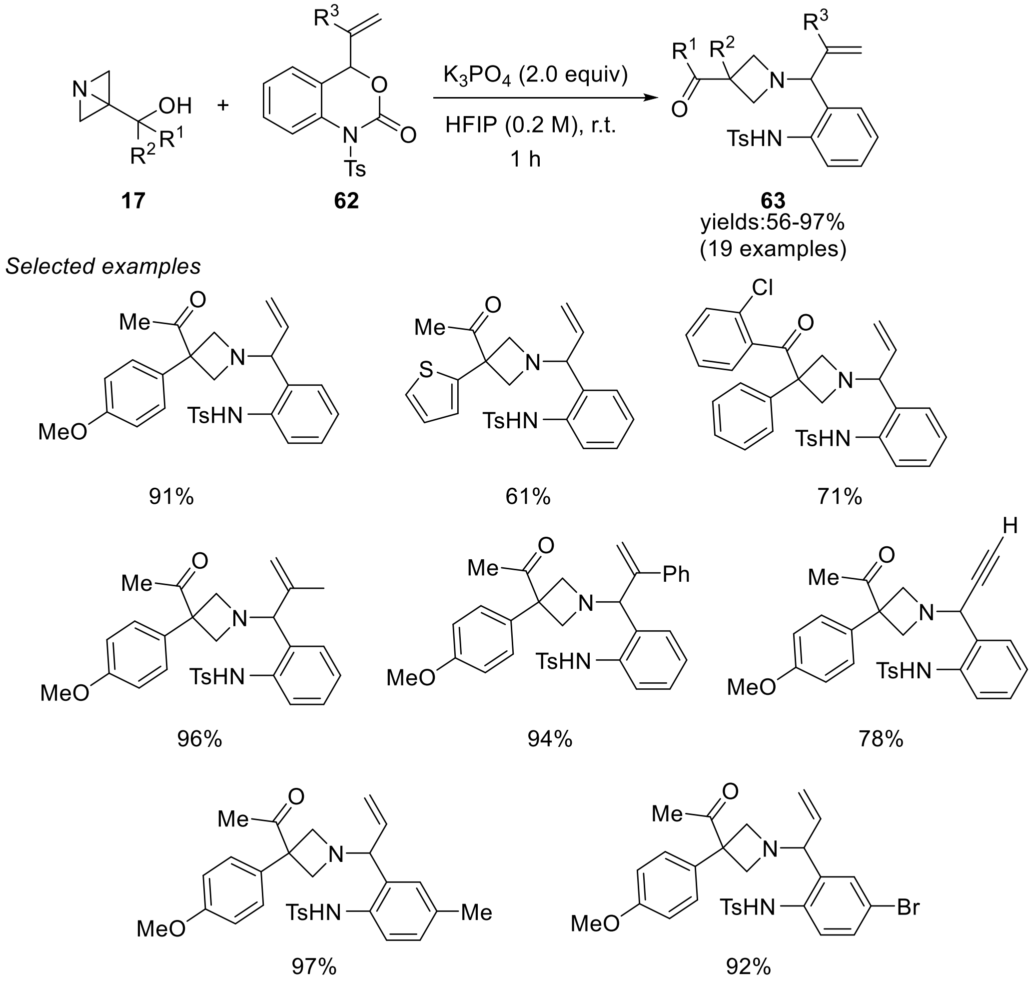
Scheme 18. Cation-driven diversity-oriented approach through N/C3 functionalization of ABB to functional azetidines.

It is worth noting that the use of other fluorinated solvents (PhCF$_3$ or TFE) or isopropanol proved futile, and the reaction did not proceed without a base. In addition, HFIP alone was found to promote semi-pinacol rearrangement of carbinol **17** to azetidine **61**. Treatment of azetidines **61** with α-halohydroxamate **59** under standard conditions did not produce any trace of azetidines **60** ruling out a stepwise process (Scheme 19).

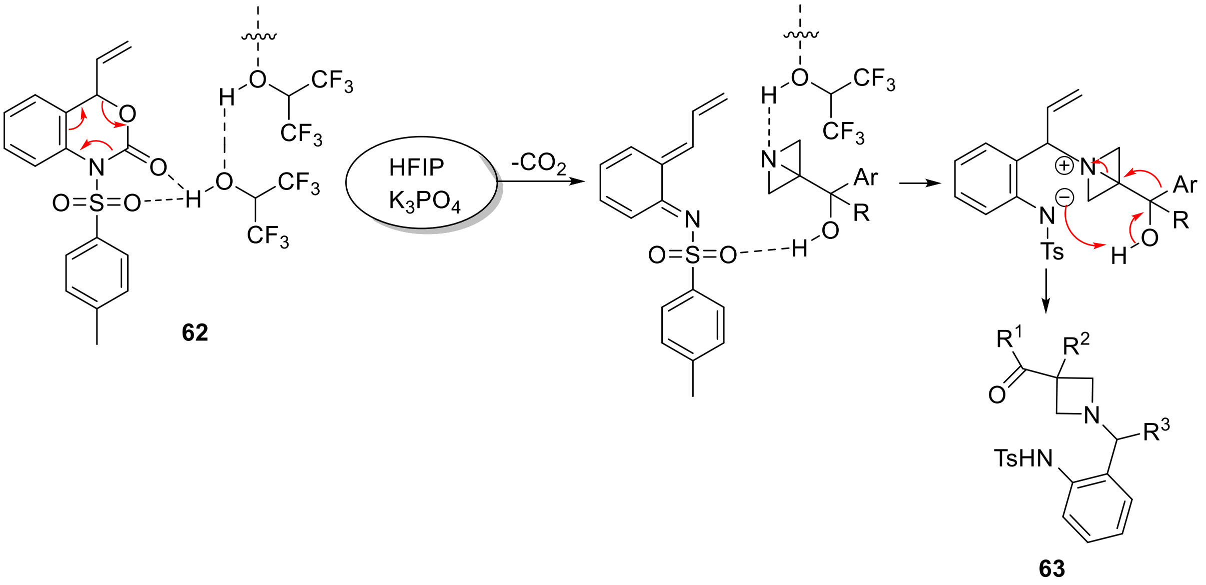


Scheme 19. An attempted stepwise synthesis of N/C3-functionalized azetidines.

An efficient ABB-based strategy engaging the reactive aza-*ortho*-quinone methides (aza-*o*-QM) to access N/C3-functionalized azetidines has been developed.[48] In this method the aza-*o*-QM **62** is generated *in situ*, orthogonally, under metal-free conditions from vinyl benzoxazinones and subsequently added to ABB **17** leading to strain-release-driven 1,3-functionalization to furnish azetidines **63** (Scheme 20). As per the suggested mechanism (Scheme 21), the combination of HFIP-K_3PO_4 is critical for orthogonal activation of aza-*ortho*-quinone methide **62** through CO_2 expulsion. Further, the authors speculated that the HFIP cluster could bring the Ts group/N-atom of the transient aza-*o*-QM and ABB-carbinol OH in close proximity, thus favoring the formation of the products **63**.



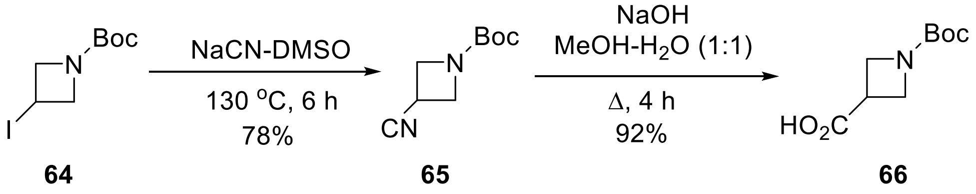
Scheme 20. An ABB-based strategy using aza-*ortho*-quinone methides (aza-*o*-QMs) to access N/C3-functionalized azetidines.



Scheme 21. A proposed reaction mechanism for Scheme 20.

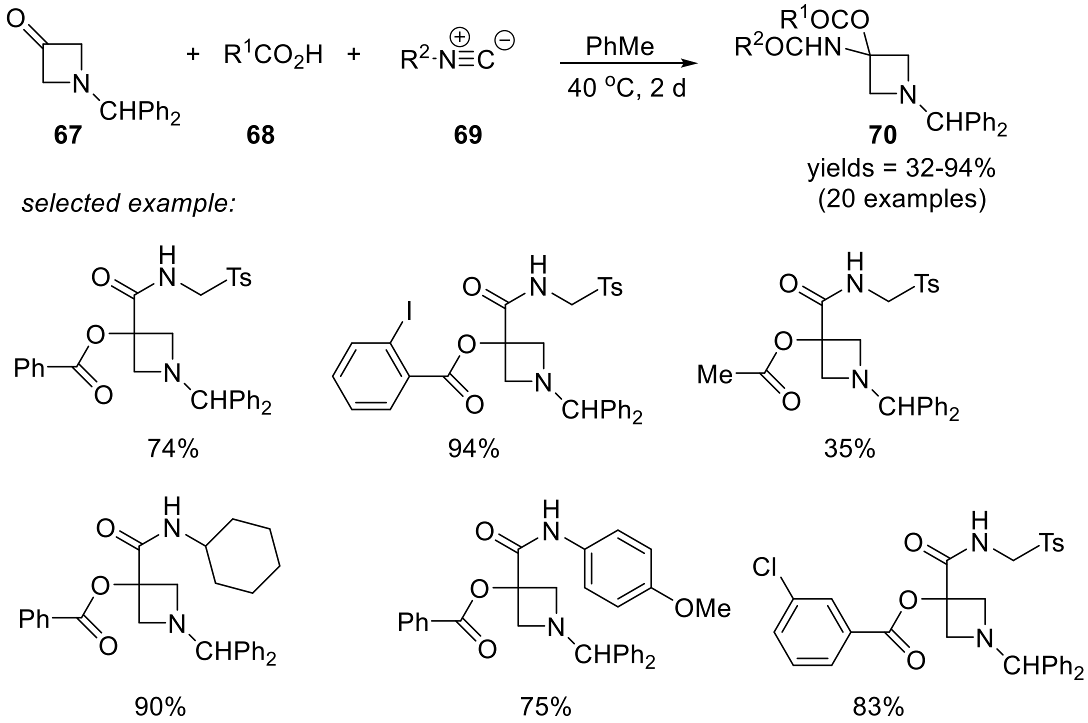
Besides ABB-based strategies, some other simple protocols have been reported for the synthesis of 3-functionalized and 3,3-difunctionalized azetidines. Cyclization of 1,3-aminoalcohols is a well-known principal method for the synthesis of azetidines.[1] In the middle of past decade, De Kimpe laboratory employed this strategy in the synthesis of azetidine-3-carboxylic acid. For example, Semina and coworkers used the osmium-catalyzed dihydroxylation of *N*-substituted alkyl 2-(aminomethyl)acrylates to access 2-(aminomethyl)-2,3-dihydroxypropanoates in good yields (82–89 %).[49] The resulting aminodiols were cyclized to synthesize the corresponding 3-functionalized azetidine-3-carboxylates by straight forward cyclization with potassium carbonate. Basic (LiOH) hydrolysis of *N*-substituted 3-azidoazetidine-3-carboxylates was reported to yield *N*-substituted 3-azidoazetidine-3-carboxylic acids.[50]

In 2018, Ji and co-workers have reported the synthesis of highly valued azetidine-3-carboxylic acids including the first reported synthesis of 1-(*t*-butoxycarbonyl)-3-((trifluoromethyl)thio)azetidine-3-carboxylic acid.[51] Treatment of *N*-Boc-3-iodoazetidine **64** (see 3-haloazetidines) with NaCN in DMSO yielded the corresponding 3-cyanoazetidine **65** in good yield on a gram-scale. Alkaline hydrolysis of **65** afforded *N*-Boc-substituted azetidine-3-carboxylic acid **66** in an excellent yield (92%) (Scheme 22).



Scheme 22. Synthesis of *N*-Boc-protected azetidine-3-carboxylic acid.

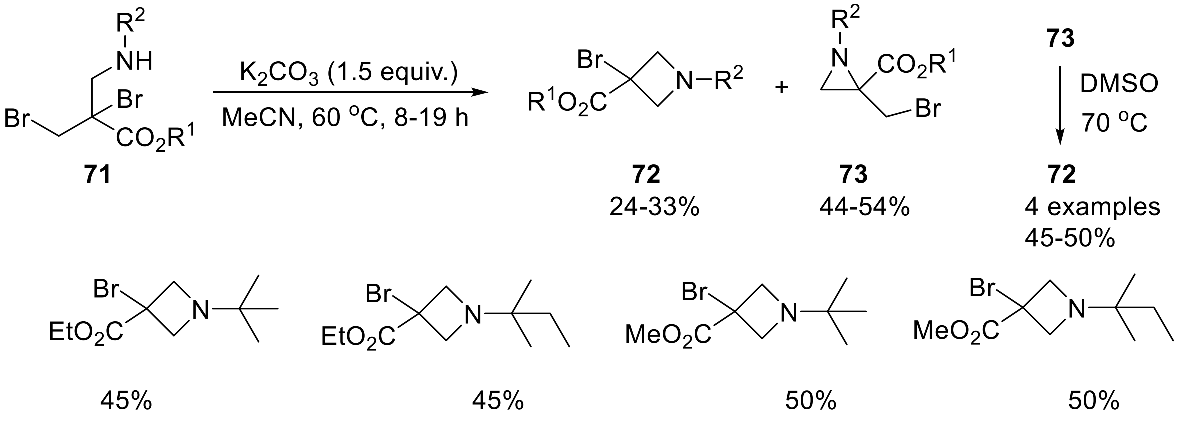
Recently, the Passereni reaction on azetidine-3-ones has been utilized to synthesize 3-acyloxyazetidine-3-carboxamides **70**.[52] Over twenty such azetidines were obtained in good to excellent yields by a three-component reaction *of* *N*-benzhydrylazetidin-3-one **67**, carboxylic acids **68** and isocyanides **69** in toluene at 40 °C for 2 days (Scheme 23). Diverse functionalities on both carboxylic acids and isocyanides were well tolerated.



Scheme 23. Synthesis of 3,3-difunctionalized azetidines using Passereni reaction.

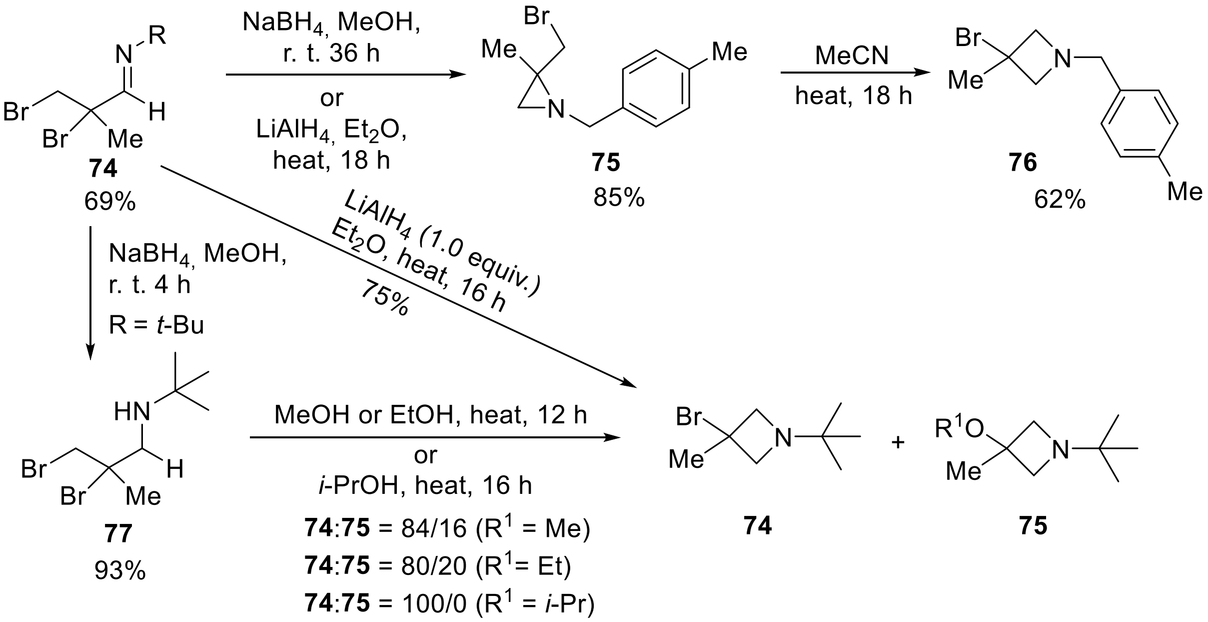
2.3. Synthesis of 3-haloazetidines

N-Protected 3-haloazetidines have been widely used as versatile building blocks in medicinal chemistry. Application of 3-iodoazetidine in the synthesis of azetidine-3-carboxylic acids is shown in Scheme 22 above. Several reports have appeared in recent literature on their synthesis and application. A report on the synthesis of *N*-substituted 3-bromoazetidine-3-carboxylates using α-bromo-α-bromomethyl-β-aminoesters **71** as precursors is published.[53] The cyclization of esters **71** on treatment with potassium carbonate in acetonitrile affords both azetidines **72** and kinetically controlled product aziridines **73** (Scheme 24). The latter compounds are also transformed to azetidines **72** by isomerization on heating in dimethyl sulfoxide. Several diversely substituted azetidine-3-carboxylates were synthesized by nucleophilic reaction of the bromo group in azetidines **72**.



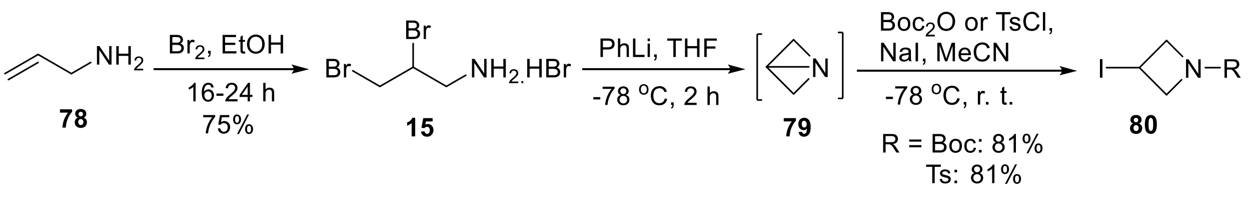
Scheme 24. Synthesis of *N*-substituted 3-bromoazetidine-3-carboxylates using α-bromo-α-bromomethyl-β-aminoesters as precursors.

The above methodology has been further explored for a facile synthesis of 1-*t*-butyl- and 1-(4-methylbenzyl)-3-bromo-3-methylazetidines as well.[54,55] The reduction of imine **74** with sodium borohydride or lithium aluminum hydride furnished aziridine **75** that got isomerized to azetidine **76** on heating in acetonitrile (Scheme 25). However, the *N*-*t*-butyl aldimine afforded the corresponding amine **77** on reduction with sodium borohydride in alcohols that cyclized to thermodynamically preferred azetidines **78** and **79** on prolonged heating in ethanol or isopropanol. An imine bearing *t*-butyl group directly afforded *N*-*t*-butyl-3-bromo-3-methylazetidine in 75% yield on treatment with lithium aluminum hydride in diethyl ether. *N*-Boc-protected 3-Bromo-3-ethylazetidine synthesized by this strategy is easily transformed to 3-alkylideneazetidine on treatment with potassium *t*-butoxide.[56]



Scheme 25. Ring-expansion of aziridine to 3-bromo-3-methylazetidine.

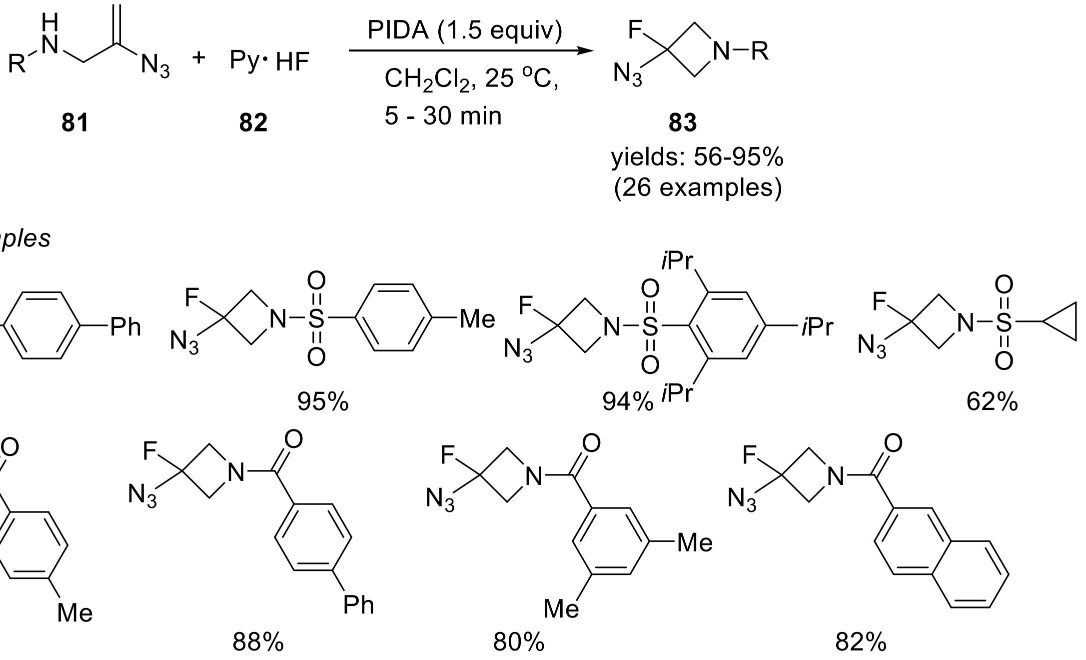
A one-pot strain-release protocol using 1-azabicyclo[1.1.0]butane, generated *in situ* from commercially available substrates, has been developed for a gram-scale synthesis of 3-iodoazetidines.[53] Allylamine **78** was reacted with an ice-cold solution of bromine in ethanol to form 2,3-dibromopropanamine hydrochloride **15** (Scheme 26). Treatment of amine hydrobromide with phenyllithium generated the azabicyclobutane **79**. The generation of carbocation at C-3 position of **77** by treatment with Boc₂O or *p*-toluenesulfonyl chloride followed by reaction with iodide afforded the *N*-substituted 3-iodoazetidines **80**.



Scheme 26. 3-Synthesis of *N*-protected 3-iodoazetidines.

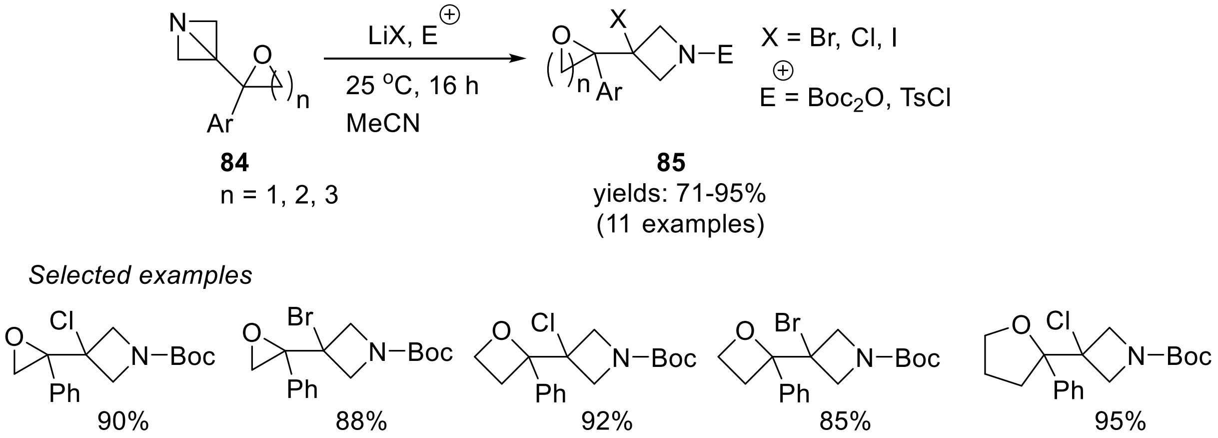
Zang and co-workers have developed an efficient method to prepare 3-functionalized azetidines by fluorocyclization of readily available 2-azidoallyl amines.[57] The method involves treatment of 2-azidoallyl amines

81 with pyridine·HF **82** in iodobenzene diacetate (PIDA) and anhydrous dichloromethane at 25 °C to furnish *N*-substituted 3-azido-3-fluoroazetidines **83** in good yields (56-95%) (Scheme 27). The electron-donating group appears to play a critical role in polarizing the C=C double bond and facilitating intramolecular cyclization.



Scheme 27. Synthesis of *N*-substituted 3-azido-3-fluoroazetidines.

A flow technology developed by Musci and co-workers enabled preparation of 3-haloazetidines **85** from C3-heterosubstituted azabicyclo[1.1.0]butanes **84**.[58] Halogenation of ABBs in the presence of an electrophile such as Boc_2O or TsCl allowed for the selective C3-N bond cleavage to furnish 3-haloazetidines in good yields (71-95%) (Scheme 28).

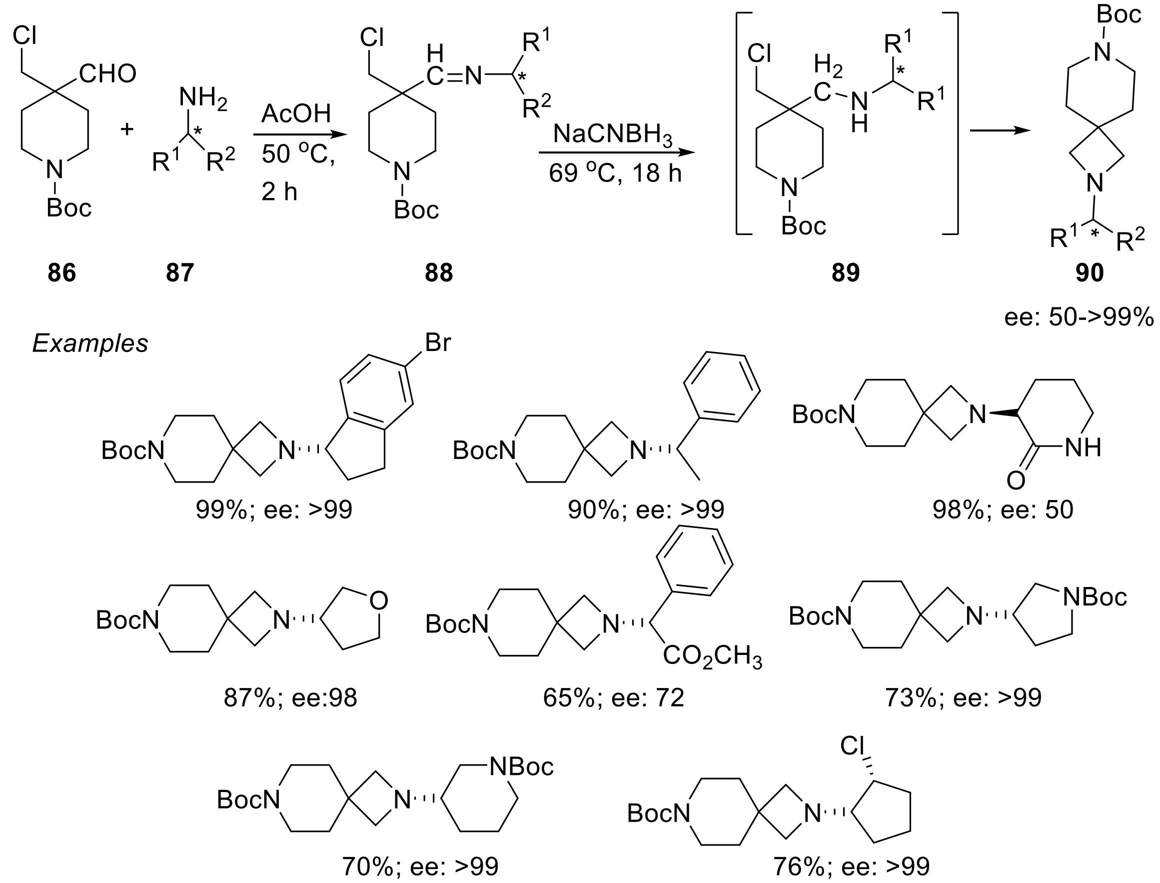


Scheme 28. Synthesis of *N*-protected 3-bromo/chloroazetidines.

2.4. Synthesis of 3-alkyl/aryl substituted azetidines

3-Vinyl- and 3-hydroxymethylazetidine motifs have been discovered from nature (Figure 1). Furthermore 3-alkylazetidines are also of biological importance (Figure 2). There are several reports in literature on synthesis of 3-alkylazetidines. The methods include cyclization of 3-haloamines, 3-aminoethers, reduction of 2-azetidinones, functional group transformation on azetidine rings, and cleavage of azabicyclobutanes.

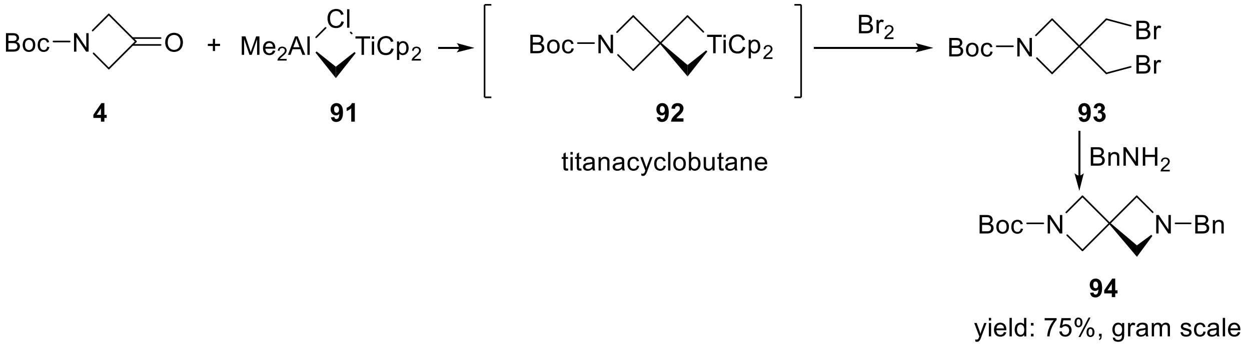
In a protocol developed by Orr and coworkers, chiral imines **88**, obtained from the condensation of *N*-Boc-substituted 4-chloromethylpiperidine-4-carboxaldehyde **86** with various chiral amines **87**, undergo reduction on treatment with sodium cyanoborohydride furnishing the corresponding γ-chloroamines **89** that cyclized under the reaction conditions leading to the formation of spiro-fused azetidines **90**.[59] Since the chiral carbon of the imines was not involved either in reduction or in cyclization, the final products retained the chiral purity of the starting amines. The products were obtained in excellent yields and in ees up to 99% (Scheme 29).



Scheme 29. Synthesis of 3-alkyl-substituted spiroazetidines.

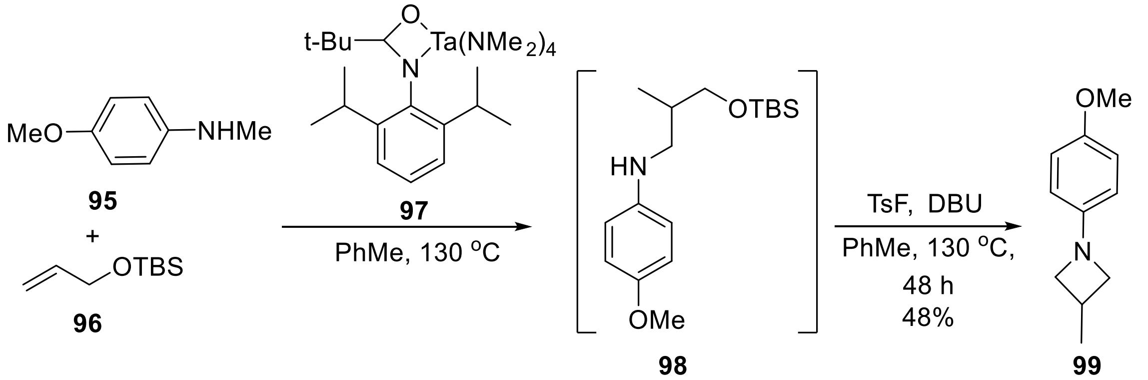
Azetidines spiro-fused to aziridine or another azetidine constitute challenging frameworks from a synthetic viewpoint. The De Kimpe group synthesized *N*-tosylazetidines spirofused at its C-3 position with carbon of *N*-substituted aziridines, 1,5-diazaspiro[2,3]hexanes in four steps starting from easily accessible ethyl 2-(bromomethyl)-1-tosylaziridine-2-carboxylate.[60] The key steps involved chemoselective reduction of the functionalized ethyl 1-tosylaziridine-2-carboxylate to the corresponding β-bromo aldehyde and an aza-Payne-type rearrangement of intermediate *N*-tosyl 2-(aminomethyl)aziridines into *N*-alkyl 2-(aminomethyl)aziridines. Finally, a base-mediated cyclization of the formed bromo amines furnished novel diazaspirocyclic motif.

Weinhold and coworkers have developed a new protocol to access novel *bis*-azetidines spirofused at C-3. Titanacyclobutanes generated from ketones or alkenes are halogenated to form alkyl dihalides that can be subsequently captured by amines to afford spiro-fused *bis*-azetidines.[61] In a representative example (Scheme 30), titanacyclobutane **92**, generated from the reaction of *N*-Boc-azetidin-3-one **4** and the titanium reagent **92**, is brominated to give alkyl dibromide **93** that is cyclized in the presence of benzylamine to yield spiro-fused *bis*-azetidine, *t*-butyl 6-benzyl-2,6-diazaspiro[3,3]heptane-2-carboxylate **94**.



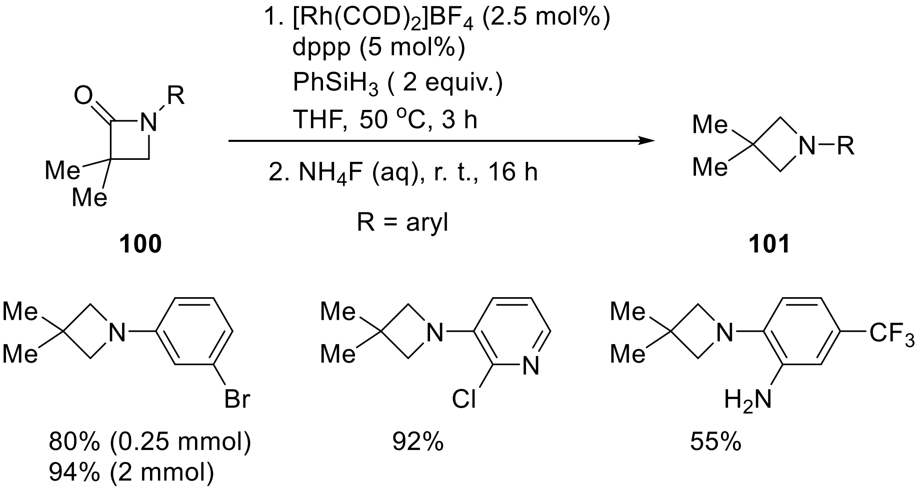
Scheme 30. Synthesis of *bis*-azetidines spirofused at C-3 using titanacyclobutane.

A protocol to synthesize 1-(4-methoxyphenyl)-3-methylazetidine **99** is reported by cyclization of 1,3-aminoether **98** in the presence of *p*-toluenesulfonyl fluoride and 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU).[62] The synthesis of the aminoether **98**, in turn, is achieved by alkylation of 4-methoxy-*N*-methylaniline **95** adjacent to the nitrogen atom using allylic ether **96** and a tantalum-based catalyst **97** (Scheme 31).



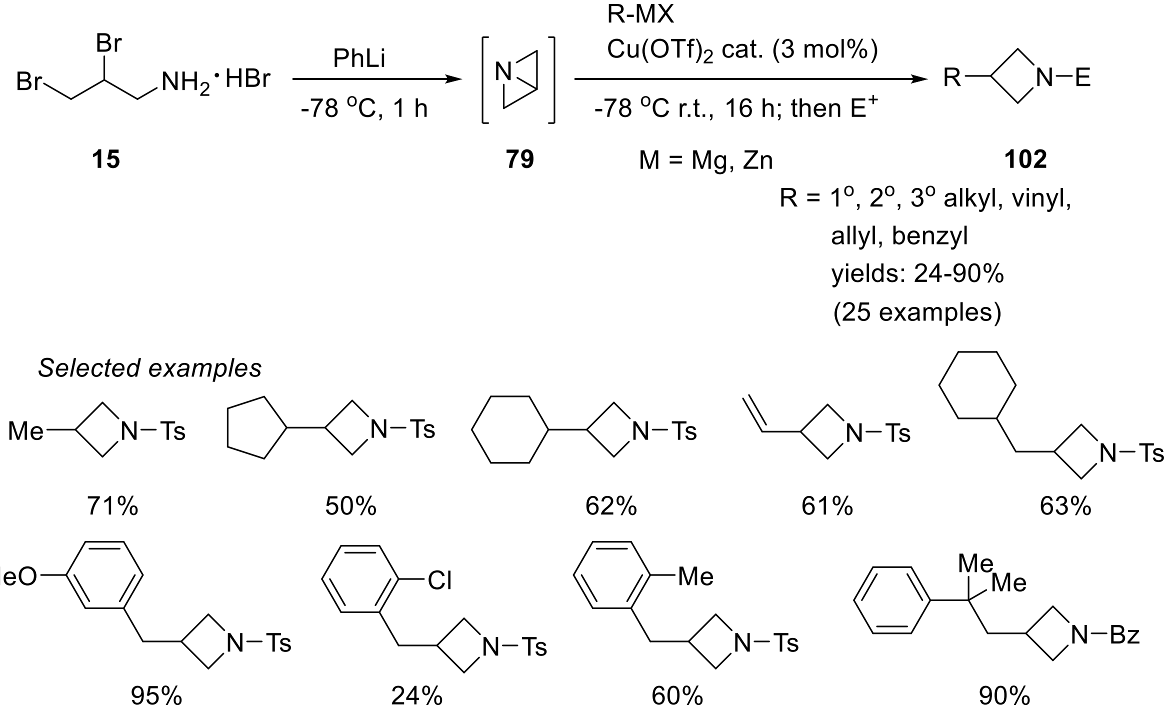
Scheme 31. Synthesis of 3-methyl-1-(4-methoxyphenyl)azetidine.

Azetidin-2-ones are reduced to azetidines with various reducing agents. Bornschein and coworkers have developed a selective Rh-catalyzed protocol for activation of phenylsilane to reduce tertiary azetidin-2-ones **100** to azetidines **101**.[63] A one-pot protocol from commercially available starting materials **100** and a selective reduction of a complex penicillin derivative demonstrated the high synthetic scope of this facile method. The combination of $[Rh(COD)_2]BF_4$ and 1,3-bis(diphenylphosphino)propane (dppp) allows the reaction to proceed rapidly under mild conditions (Scheme 32).



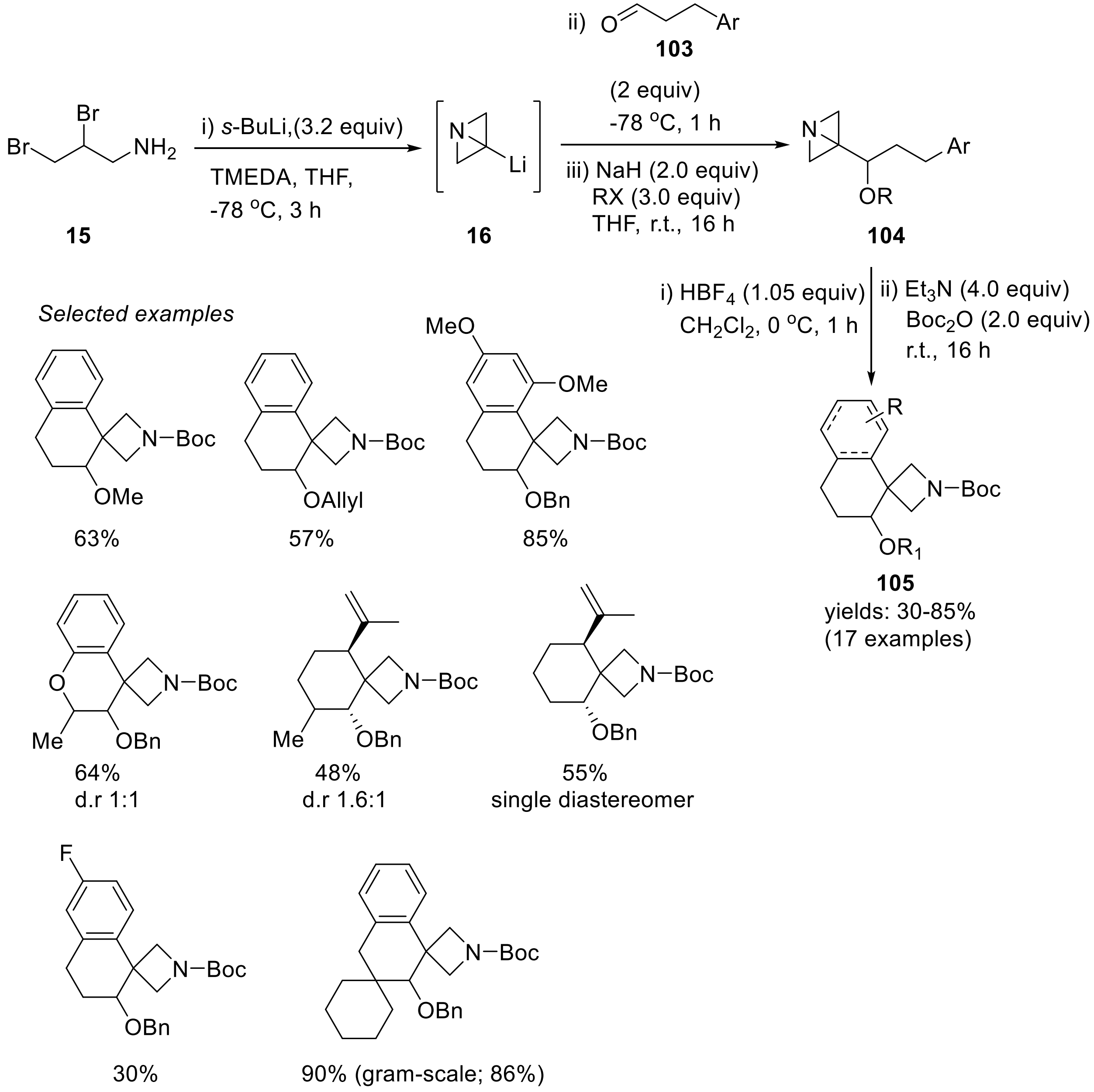
Scheme 32. Synthesis of *N*-aryl-3,3-dimethylazetidines.

Gianatassio and Kadish reported a transition-metal-catalyzed synthesis of *bis*-functionalized 3-substituted azetidines **102** from the reaction of ABB **79** with organometallic reagents in the presence of Cu(OTf)$_2$.[64] The method allows for the preparation of 3-alkyl, allyl, vinyl, and benzyl azetidines. 1-Azabicyclo[1.1.0]butane **79** was generated *in situ* by reacting 2,3-dibromopropylamine hydrobromide **15** with phenyl butyl lithium (Scheme 33). It is worth noting that attempts to functionalize 1-azabicyclo[1.1.0]butane with *t*-BuLi, *t*-BuZnBr, and *t*-BuMgCl in the absence of catalyst led to either no reaction or trace observable product, while attempts to functionalize 1-azabicyclo[1.1.0]butane with phenylmagnesium bromide (and other aryl metal reagents such as organozinc and organolithium compounds) led to isolation of complex mixtures that contained the desired product.



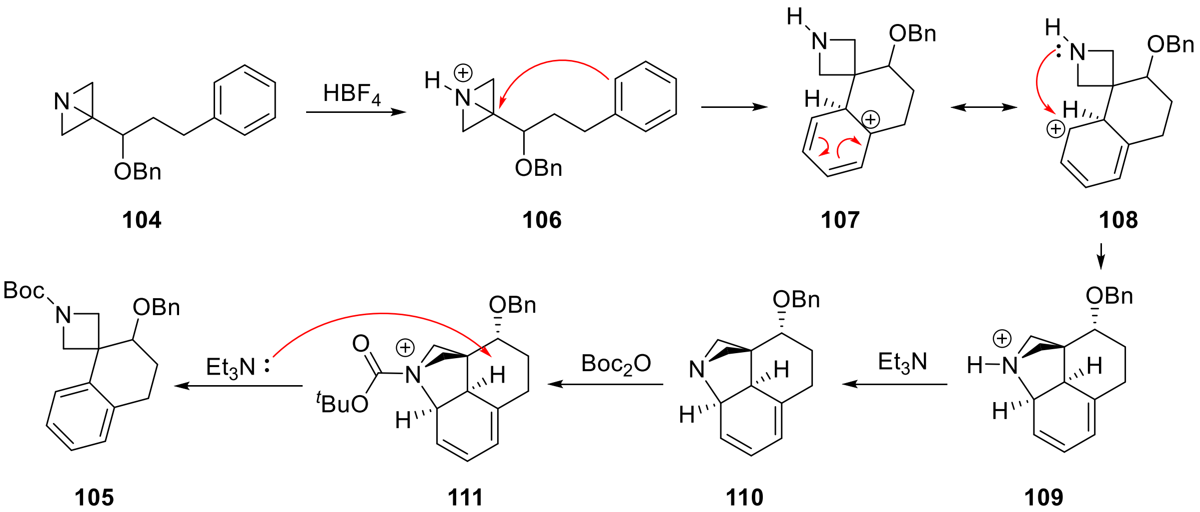
Scheme 33. Synthesis of *N*-substituted 3-alkylazetidines.

A novel strain-release-driven Friedel-Crafts spirocyclization of ABB-tethered (hetero)aryls in presence of HBF_4 to furnish azetidine spiro-tetralins has been reported by the Aggarwal group.[65] In this method, spirocyclization precursors **104** were obtained through the reaction of aryl-tethered aldehydes and ketones **103** with ABB-Li **16**, generated *in situ* from 2,3-dibromopropylamine **15**. An HBF_4-mediated Friedel-Crafts spirocyclization of **104** yielded the corresponding azetidine spirocycles **105** (Scheme 34). It was noted that although $In(OTf)_3$ has been reported as an effective Lewis acid catalyst for intramolecular Friedel-Crafts reactions,[66] no detectable product was formed in this case. In addition, an attempt of generating the Friedel-Crafts product directly from the reaction of **104** with Boc_2O and Et_3N in the absence of HBF_4 failed, clearly indicating that the spirocyclization reaction is initially promoted by the addition of the Brønsted acid.



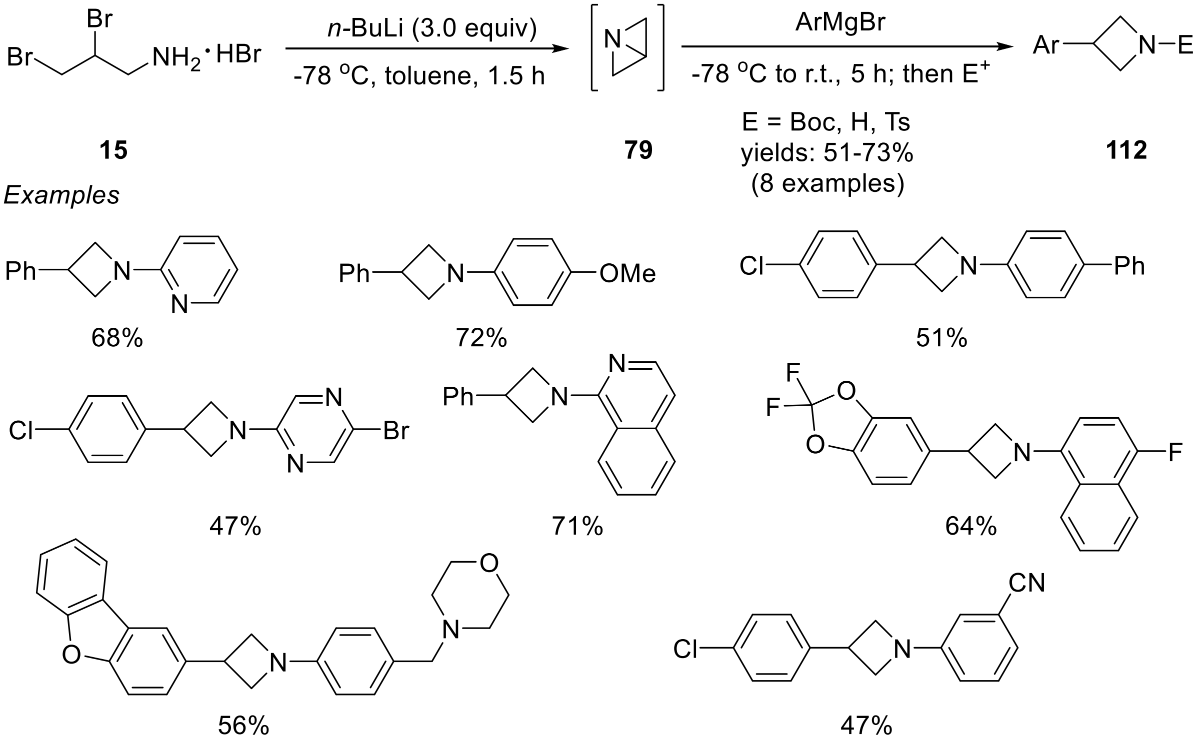
Scheme 34. Synthesis of spiro-fused azetidines.

A tentative mechanism suggests that protonation of the nitrogen in ABB **104** by HBF_4 activates the C3-N bond allowing the aryl fragment in **106** to add to the C3 of ABB system according to a Friedel-Crafts reaction. The proximity of the newly formed azetidine to the resulting cationic Wheland intermediate **107** facilitates intramolecular C-N bond formation in **108**, generating the bicyclic intermediate **109**. Treatment with Et_3N and subsequent carbamoylation with Boc_2O activates the scaffold towards C-N bond cleavage and rearomatization to afford the Friedel-Crafts spirocyclic products **105** *via* intermediates **110** and **111** (Scheme 35).



Scheme 35. Strain-release-driven Friedel-Crafts spirocyclization of Azabicyclo-[1.1.0]-butanes.

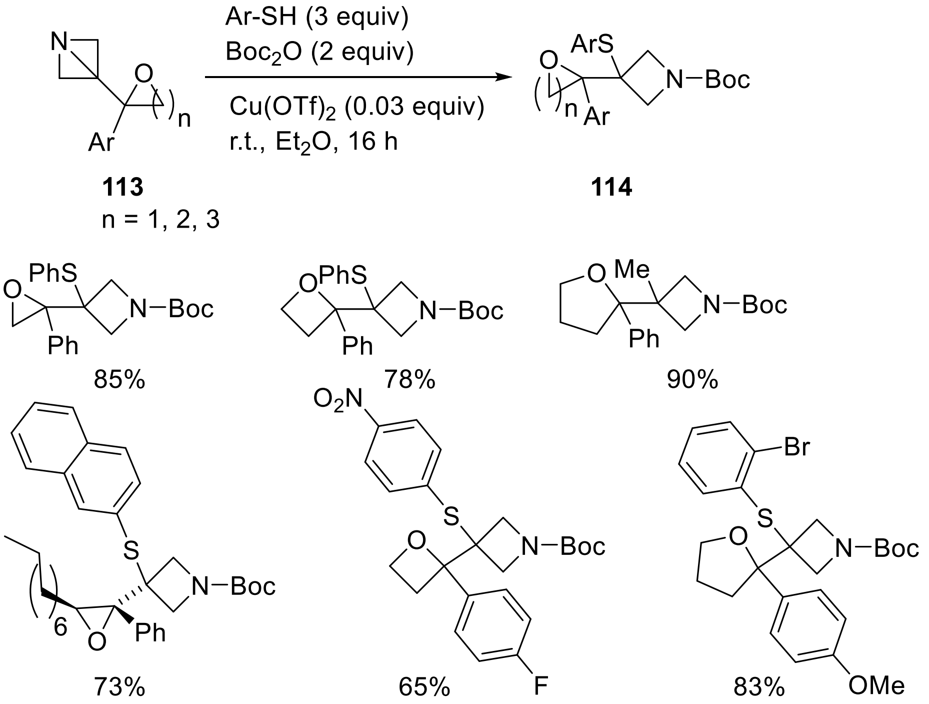
Trauner *et al.* reported a method that utilizes the nucleophilic reaction of Grignard reagents with 1-azabicyclo[1.1.0]butane **79**, generated *in situ* from 2,3-dibromopropylamine hydrobromide **15**, to access 3-arylazetidines **112** through strain-release (Scheme 36).[67] In comparison to previous approaches of generating the ABB system, this approach used the less nucleophilic *n*-BuLi as the lithiation agent instead of PhLi and toluene as the solvent to precipitate LiBr generated after the Li/Br exchange reaction, modifications which allowed for the generation of a series of 3-arylated azetidines.



Scheme 36. Synthesis of *N*-substituted 3-arylazetidines.

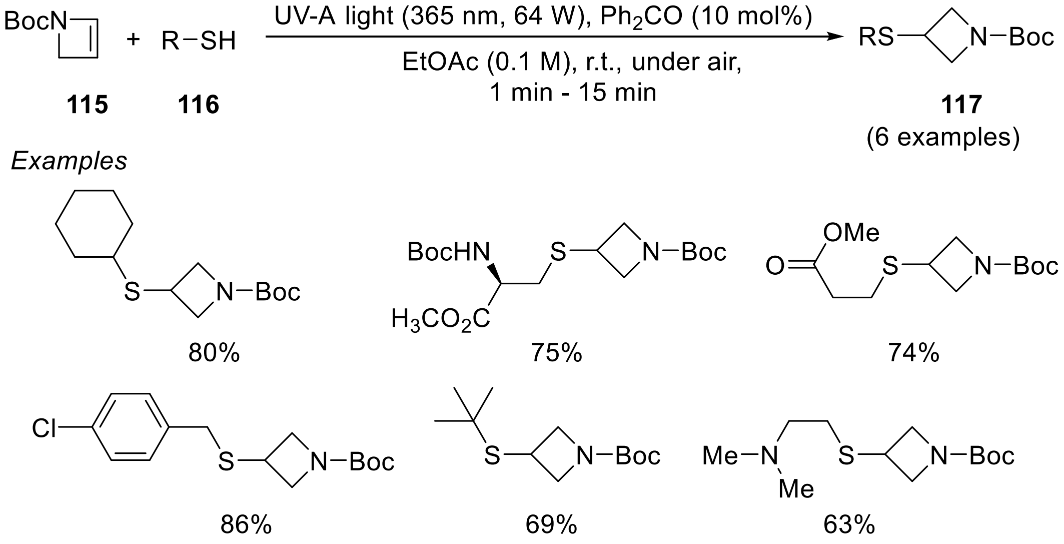
2.5. Synthesis of *t*-butyl (3-arylthio/alkylthio)azetidine-1-carboxylates

To the best of our knowledge, two reports appeared in literature on the synthesis of this scarce class of compounds. A flow method developed by Musci and co-workers enabled preparation of 3-(alkyl/arylthioazetidine)-1-carboxylates **114** from C3-heterosubstituted azabicyclo[1.1.0]butanes **113**.[58] C3-thiolation of ABBs by aromatic thiols upon copper catalysis allowed for selective cleavage of the C3-N bond of the ABB system to furnish the products in good yields (65-90%) (Scheme 37).



Scheme 37. Synthesis of 3-heterosubstituted *N*-Boc-3-methyl/arylthioazetidines.

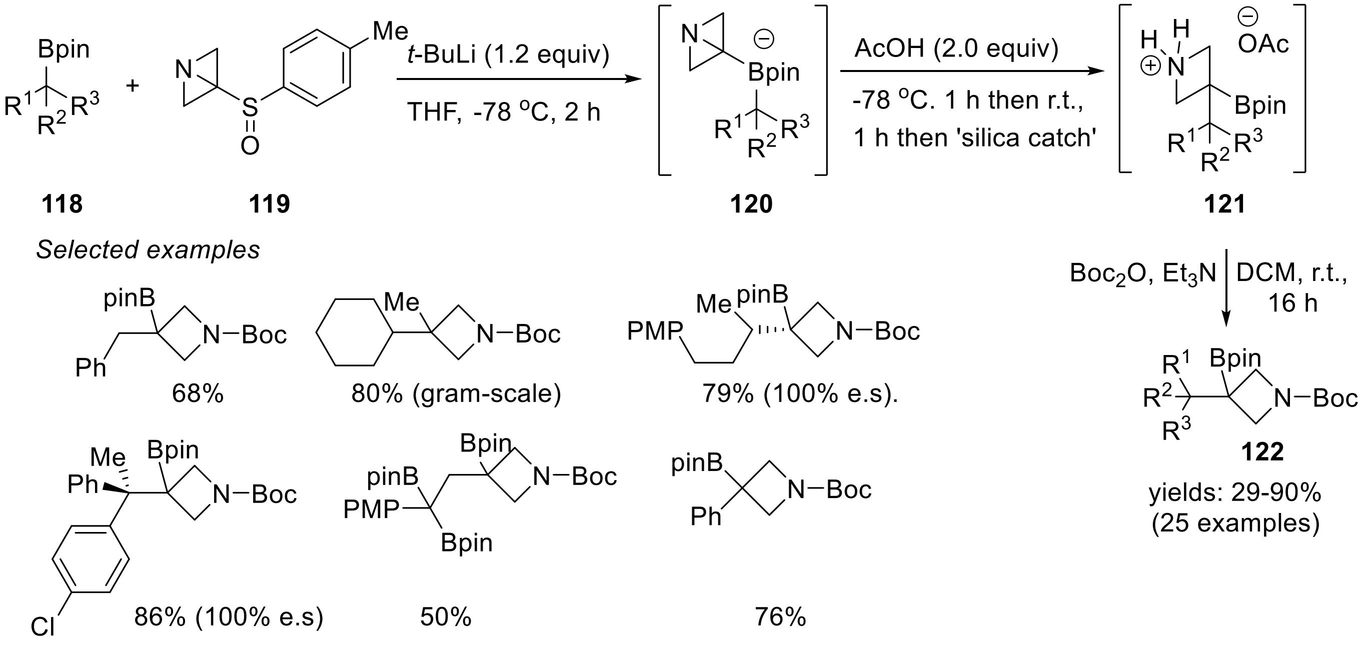
A light-mediated *anti*-Markovnikov hydrothiolation of *t*-butyl azete-1(2*H*)-carboxylate **115** in the presence of benzophenone as a photocatalyst and using thiols **116** to access 3-functionalized azetidines **117** has been developed (Scheme 38).[68]



Scheme 38. A light-mediated synthesis of 3-alkyl/arylthioazetidines.

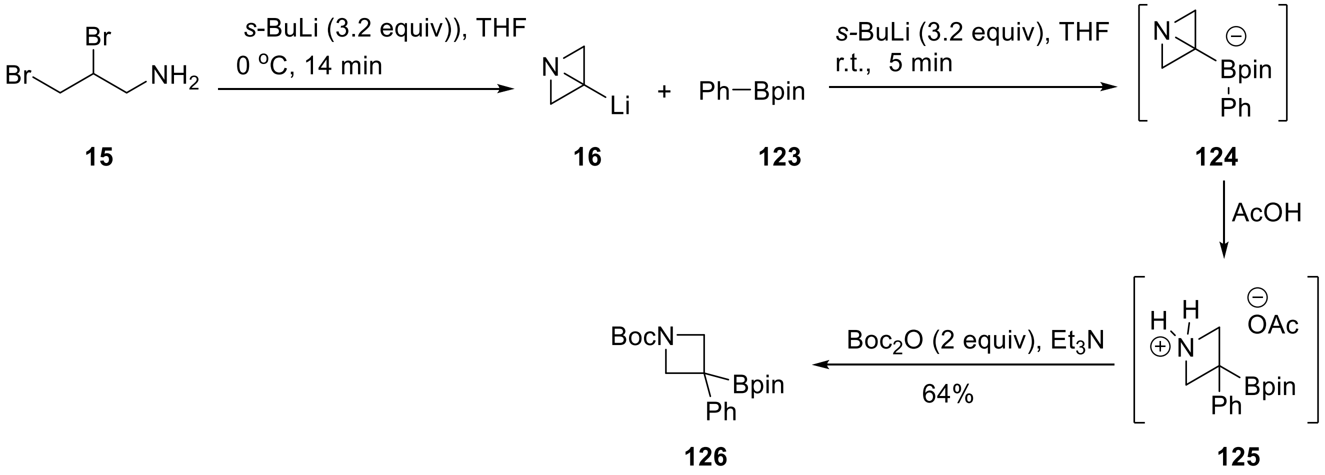
2.6. Synthesis of 3-boronic ester substituted (3-alkyl/cycloalkyl/aryl)azetidines

The cleavage of highly strained azabicyclo[1.1.0]butane for the synthesis of azetidines developed by the Aggarwal group has also been employed for the synthesis azetidines bearing boronic ester group.[31] First, azabicyclo[1.1.0]butyl lithium is generated *in situ* by reacting azabicyclo[1.1.0]butyl sulfoxide **119** with *t*-butyl lithium and trapped with a boronic ester **118** to give an intermediate boronate complex **120** which, upon N-protonation with acetic acid, undergoes 1,2-migration with cleavage of the central C-N bond to relieve ring strain giving **121**. Boc protection of **121** gives homologated azetidine boronic ester products **122** in 29-90% (Scheme 39). The method is applicable to primary, secondary, tertiary, aryl and alkenyl boronic esters, and occurs with complete stereospecificity.



Scheme 39. Synthesis of boronic ester substituted azetidines.

Musci and co-workers modified the method in Scheme 39 by Aggrawal's group by conducting the reaction under continuous flow conditions and using a solution of phenylboronate (PhBpin) **123** as the electrophile feed, allowing the entire sequence consisting of intramolecular cyclization, C3-lithiation, electrophilic trapping and strain release *via* 1,2 B to C migration *via* intermediates **124** and **125** to be accomplished in a one-pot fashion to obtain functionalized azetidine **126** in 64% yield (Scheme 40).[69]

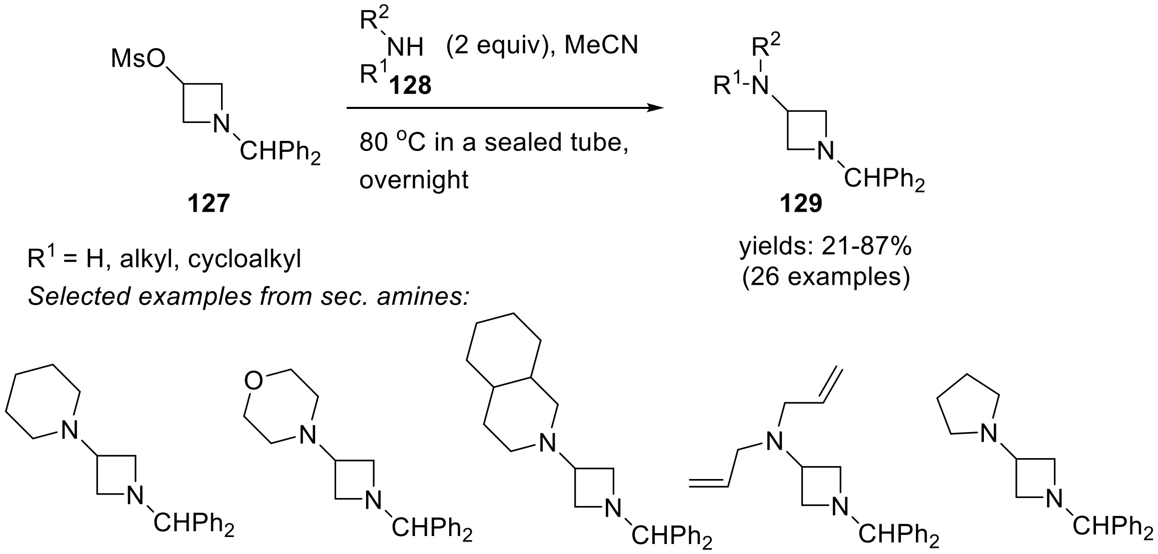


Scheme 40. Synthesis of boronic ester substituted azetidine under continuous flow conditions.

2.7. Synthesis of 3-amino/3-nitro/3-azidoazetidines

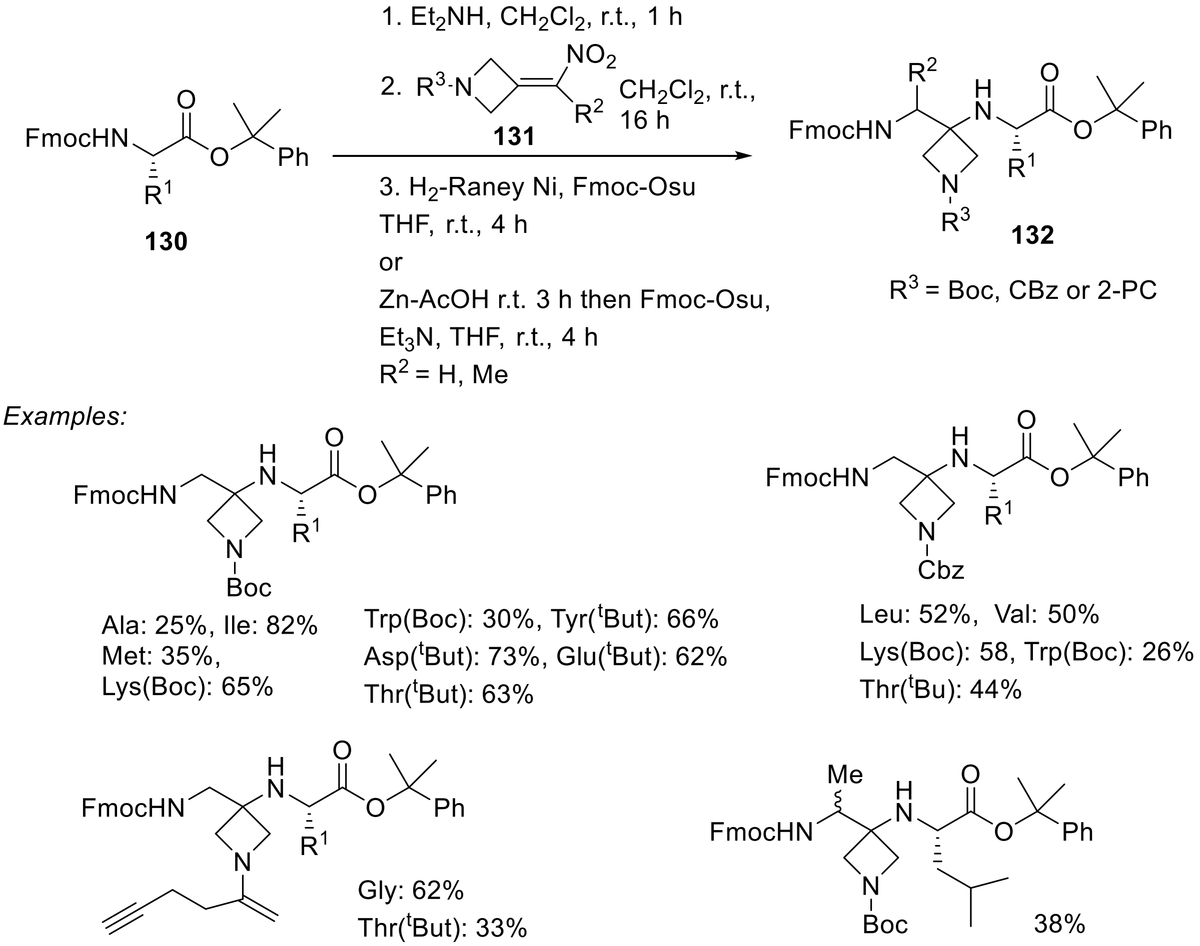
Azetidines bearing nitrogen functionalities in their C-3 position are long known motifs. 3-Aminoazetidines with antibacterial activity were reported in the 1990s.[70-74] 3-Aminoazetidine moiety are also reported as macrolide antibiotics, triple reuptake inhibitors and kinase inhibitors amongst others.[75-77] Karikomi and De Kimpe reported the synthesis of 3-aminoazetidines by a ring-opening of 1-arylsulfonyl-2-(halomethyl)aziridines with aliphatic amines in 2000.[78] The synthesis of 3-nitroazetidines was reported by Rai and Yadav in 2011.[79] Their method involved annulation of Baylis–Hillman alcohols and their aldehydes with either *N*-aryl/tosylphosphoramidates or *N*-aryl/tosylphosphoramidates in combination with a task-specific ionic liquid.

In browsing through the recent literature, we came across two novel protocols for the synthesis of 3-aminoazetidines. In 2020, Wang and Dunction reported a single step synthesis of 3-aminoazetidines.[80] 1-Benzhydrylazetidine-3-yl methane sulfonate **127**, obtained from 1-benzyhydryl-3-azetidinol was reacted with various amines **128** to yield 1-benzhydryl-3-aminoazetidines **129** (Scheme 41). The reaction tolerated common functional groups and furnished moderate-to-high yields with secondary amines, and moderate-to-low yields with primary amines.



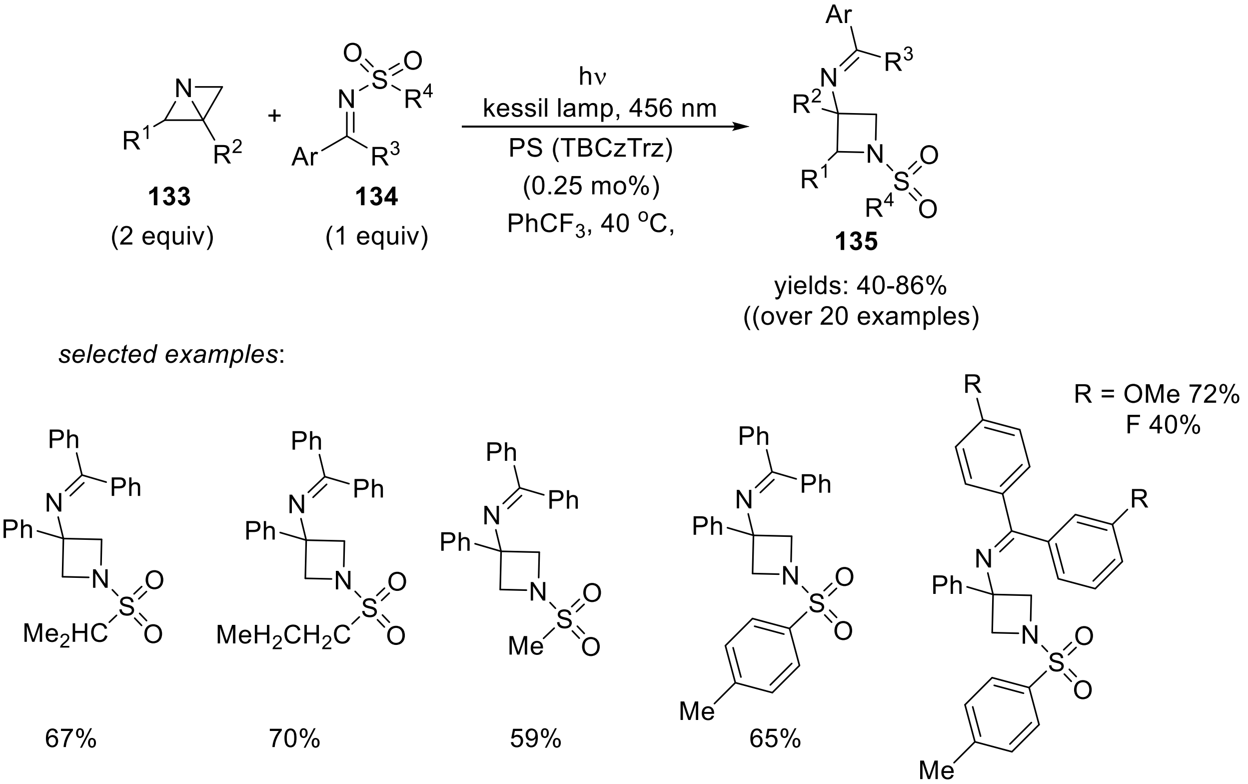
Scheme 41. Synthesis of *N*-benzhydryl-3-aminoazetidines.

Saunders *et al*. reported an efficient synthesis of small head-to-tail cyclic peptides by an improved cyclization of several tetra-, penta- and hexapeptides under standard reaction conditions.[81] This group introduced 3-aminoazetidine subunit as a new turn-inducing element within the linear peptide precursors. The 3-aminoazetidine ring did not degrade even during the deprotection of peptides after cyclization. The protocol for the synthesis of peptide containing 3-aminoazetidine started with conjugate addition of *N*-protected α-amino esters **130** to *N*-protected 3-(nitromethylene)azetidines **131**, prepared according to reported method.[82] A simultaneous reduction of the nitro group with H_2-Raney nickel or Zn-AcOH with concomitant Fmoc protection of the *N*-terminus afforded the dipeptide products **132** (Scheme 42).



Scheme 42. Synthesis of peptides containing *N*-Boc-3-aminoazetidine moiety.

Rodriguez and coworkers have developed a photocatalyzed sulfoimination of ABBs for the synthesis of *N*-sulfonyl-3-sulphonylimino-3-arylazetidines (Scheme 43).[83] The radical intermediates were trapped by the azabicyclo[1.1.0]butanes *via* a radical strain-release process, furnishing 3,3-difunctionalized azetidines in a single step. 9,9,9-(5-(4,6-diphenyl-1,3,5-triazin-2-yl)benzene-1,2,3-triyl)tris(3,6-di-*t*-butyl-9*H*-carbazole) (TBCzTrz) was used as a photosensetizer. This radical process was studied by a combination of spectroscopic and optical techniques and DFT calculations. Several novel azetidines were synthesized including derivatives of celecoxib and naproxen, the well-known nonsteroidal anti-inflammatory drugs.



Scheme 43. Synthesis of *N*-sulfonyl-3-aryl-3-iminoazetidines by a photocatalyzed sulfoimination of ABBs.

As the most recent update we would like to mention here an easy and straightforward synthesis of several *N*-Boc protected 3,3-difunctionalized azetidines including 3-amino-3-arylazetidines by Wang and Zhang.[84] In this methodology, *N*-Boc protected 3-arylazetidine-3-trichloroacetimidates are treated with diverse nucleophiles like amines, alcohols, phenols, and thiols in the presence of $Sc(OTf)_3$ (10 mol%) to yield 3,3-difunctionalized azetidines.

3. Concluding Remarks

3-Functionalized azetidines have been recognized as a prominent class of compounds due to their occurrence in natural products and biological activity. They are also of potential interest as building blocks for the synthesis of diverse class of ring-opened products. However, the synthesis of azetidines has always been a challenging endeavour for synthetic organic chemists due to ring strain associated with it. The synthetic studies focused on 3-functionalized azetidines appear to get momentum after pioneering studies by the De Kimpe group in Belgium and then the Yadav group in India. In recent years, the Aggarwal group has widely employed ring-strain release strategy starting from aziridines or from azabicyclobutanes for the synthesis of diversely functionalized azetidines.

3-Hydroxy/alkoxyazetidines have been synthesized by cyclization of 3-bromoamines, reduction of 2-azetidinones, ring-opening reactions of epichlorohydrin with amine nucleophiles, and *via* azacyclobutanes from aziridines. The reaction of azabicyclobutyllithium with ketones forming the corresponding carbinol and ring-opening serves as a powerful tool to synthesize 3-carbonylazetidines that is evident from several reports in literature. Nucleophilic substitution of *N*-Boc-3-iodoazetidine has been employed for the synthesis of *N*-Boc-azetidine-3-carboxylic acid. For the 3-haloazetidines, syntheses of 3-fluoro-, 3-chloro-, 3-bromo-, and 3-

idoazetidines are reported in literature. Appropriately substituted aziridines and azabicyclobutanes have been employed as precursors. An interesting synthesis of 3-fluoroazetidine-3-azide is reported by fluorocyclization of readily available 2-azidoallyl amines. Several3-alkyl/arylazetidines have been accessed by cyclization of γ-chloroamines and γ-aminoethers. Reduction of suitably substituted 2-azetidinones and strain-release strategy of azabicyclobutane has also been explored for the synthesis 3-alkyl/arylazetidines. A light-mediated *anti*-Markovnikov hydrothiolation of *t*-butyl azete-1(2*H*)-carboxylate using thiols in the presence of benzophenone as a photocatalyst is reported to yield 3-sulfur-substituted azetidines. Interestingly, an azetidine series having boronic ester moiety on its C-3 position has also been synthesized. A protocol for the synthesis of peptides containing 3-aminoazetidine starting with conjugate addition of *N*-protected α-amino esters to *N*-protected 3-(nitromethylene)azetidines has been developed. *N*-benzhydryl-3-aminoazetidines have also been synthesized by nucleophilic substitution of *N*-benzhydryl-3-mesyloxyazetidines with amines. Most recently, a photocatalyzed sulfoimination of ABBs has been developed for the synthesis of *N*-sulfonyl-3-sulphonylimino-3-arylazetidines.

It is, thus, evident from the review of recent literature that studies on diverse 3-functionalized azetidines have attracted significant interest of synthetic organic chemists. Many interesting studies are anticipated in the future.

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